FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF VENLAFAXINE HYDROCHLORIDE

A Dissertation Submitted to

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In partial fulfillment for the award of Degree of

MASTER OF PHARMACY

(Pharmaceutics)

Submitted by

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(Accredited By "NAAC" with CGPA of 2.74 on a Four point Scale at "B" Grade)

MELMARUVATHUR - 603 319

APRIL 2013

CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF VENLAFAXINE HYDROCHLORIDE**" submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **ARCHANA.M (Register No. 26116001)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2012-2013.

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CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF VENLAFAXINE HYDROCHLORIDE**" the bonafide research work carried out by **ARCHANA.M (Register No. 26116001)** in the Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur which is affiliated to The Tamil-Nadu Dr. M.G.R. Medical University under the guidance of **Dr. S. SHANMUGAM, M. Pharm., Ph.D.,** Professor, Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur.

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Dedicated to

My beloved

Parents & Friends...

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ARCHANA.M

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ABBREVIATION AND MEANING

%	Percentage
%DE	Percentage dissolution efficiency
µ	Micron
µg/ml	Microgram per milliliter
^{0}C	Degree Celsius
Cm^{-1}	Centimeter inverse
C_{max}	Peak plasma concentration
BP	British Pharmacopoeia
DSC	Differential scanning calorimetry
e.g.	Example
Edn	Edition
F	Formulation
F/C	Film coated
FTIR	Fourier transform infrared spectroscopy
g/ml	gram per milliliter
GIT	Gastro intestinal tract
HCl	Hydrochloric acid

Hrs	Hours
ICH	International conference on harmonization
IP	Indian pharmacopoeia
Kg/cm^2	kilogram per centimeter square
LBD	Loose bulk density
MDT	Mean dissolution time
Mg	Milligram
Ml	Millilitre
ml/min	millilitre per minute
Mm	Millimeter
N	Normality
NaOH	Sodium hydroxide
NF	National formulary
Nm	Nanometer
^{o}	Degree
pH	Negative logarithm of hydrogen ion
pKa	Dissociation constant

Qs	Quantity sufficient
RH	Relative humidity
Rpm	Revolution per minute
S.No.	Serial number
SD	Standard deviation
SR	Sustained release
$t_{1/2}$	Biological half life
TBD	Tapped bulk density
T_{max}	Time of peak concentration
USP	United states pharmacopoeia
UV	Ultraviolet
w/w	weight per weight
λ_{max}	Absorption maximum

INTRODUCTION

1.INTRODUCTION

1.1. Oral drug delivery system: *(Banker G.S. and Rhodes C.T., 2009; Chein Y.W., 2009; http://www.pharmainfo.net)*

Oral route has been the commonly adopted and most convenient route for the drug delivery. Oral route of administration has been received more attention in the pharmaceutical field, because of the more flexibility in the designing of dosage form than drug delivery design for other routes. The oral drug delivery depends on various factors such as type of delivery system, the disease being treated, the patient, the length of the therapy and the properties of the drug. Most of the oral controlled drug delivery systems (OCDDS) relay on diffusion, dissolution, or combination of both mechanisms, to release the drug in a controlled manner to the gastro intestinal tract (GIT). The physico-chemical properties include crystal nature, solubility, partition coefficient, intrinsic dissolution, etc. dosage form characteristics are controlled and optimized with respect to the physico-chemical properties of the drug and relevant GI environmental factors. Other factors need to be considered are diseased state, the patient compliance & length of therapy. The goal of targeted oral drug delivery systems is to achieve better therapeutic success compared to conventional dosage form of the same drug. This could be achieved by improving the pharmacokinetic profile, patient convenience and compliance in therapy.

Oral route of drug delivery has been known for decades as the most to a wide extent used route of administration among all the routes that have been travel through to learn about it the systemic delivery of drugs via various pharmaceutical manufactured products of various dosage forms.

Oral route of administration has been used as either conventional or novel drug delivery system. There are many merits are there for this, not the least of which would include willingness to accept by the patient and facility of administration. Types of sustained release system employed for oral route of administration include virtually every at the present time now the theoretical mechanism for such application. This is because the manufacturing of dosage form is more flexibility, since constraint, such as sterility problem and potential damage at the site of administration are minimized. Because of this, it is easy to development of different types of dosage forms by customary those developed for oral route of administration as initial examples.

Regarding orally administered drugs, targeting is not a primary concern, and it is usually done on purpose for active component to permeate to the blood circulation and permeation through the other body tissue (the obvious exception being medication intended for local gastrointestinal tissue treatment). For this justification, most system employed the sustained release variety.

Concentration of drug level it will increasing the rate absorption region and also, increase circulating blood levels, which in turn to raise to greater concentration of active content at the site of action.

1.2. Drawbacks of Conventional Dosage Forms: *(Brahmankar D.M. and Jaiswal S.B., 2009; Shalin A. Modi, et al., 2011)*

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.

3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.

4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

1.3. Sustained release drug delivery system: *(Banker G.S. and Rhodes C.T., 2009; http://www.pharmainfo.net)*

Over past 30 year as the expanse and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist.

The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting, the goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. Sustained release constitutes any dosage form that provides medication over and extended time. Controlled release, however, denotes that the system is able to provide some actual therapeutic control, whether this is of a temporal nature, spatial nature or both.

This correctly suggests that there are sustain release system that cannot be considered controlled release system. In general, the goal of a sustained release

dosage form is to maintain therapeutic blood or tissue levels of drug for an extended period this is usually accomplished by attempting to obtain zero-order release from the dosage form; zero-order release constitutes drug release from the dosage form. Sustained release systems generally do not attain this type of release and provides drug is a slow first order fashion. In recent year sustained release dosage forms continue to draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Sustained release technology is relatively cow field and as a consequence, research in the field has been extremely fertile and has produced many discoveries.

Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

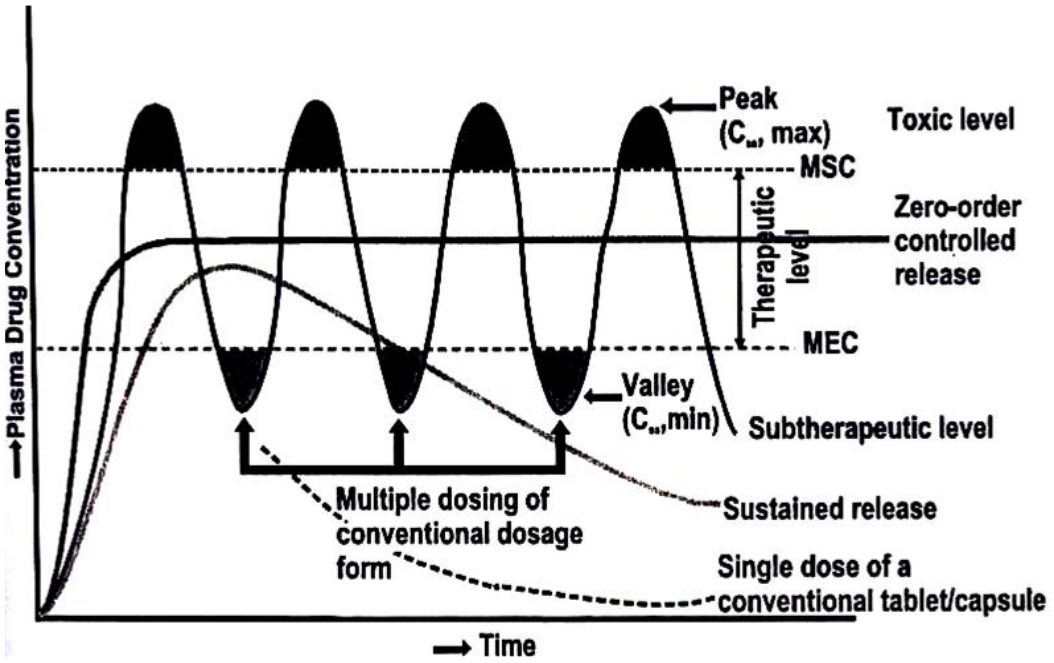


Figure 1.1: Plasma concentration versus time profile from conventional dosage and doses of sustained and controlled delivery formulation.

Systems that are designed as prolonged release can also be considered as attempts at achieving sustained-release delivery. Repeat action tablets are an alternative method of sustained release in which multiple doses of drug are contained within a dosage form, and each dosage is related to a periodic interval. Delayed release systems, in contrast may not be sustaining, science often function of these dosage forms is to maintain the drug within the dosage form for some time before release. Commonly the release rate of drug is not altered and does not result in sustained delivery once drug release has begun.

Successful fabrication of sustained release products is usually difficult & and involves consideration of physicochemical properties of drug, pharmacokinetic behavior of drug, route of administration, disease state to be treated and, most importantly, placement of the drug in dosage form total will provide the desired temporal and spatial delivery pattern for the drug.

The slow first order release obtained by a sustained release pre parathion is generally achieved by the release of the drug from a dosage form. In some cases in some cases, this achieved by making slow the release of drug from a dosage form. In some cases, this is accomplished by a continuous release process.

1.3.1. Potential advantages of Sustained release drug delivery system:

(http://www.pharma info.net)

1. Patient compliance due to reduction in the frequency of designing.
2. Employ minimum drug.
3. Minimize or eliminates local and systemic side effects.
4. Obtain less potentiating or deduction in drug activity with chronic use.
5. Minimize drug accumulation with chromic dosing.

6. Improves efficacy in treatment.
7. Cure or control confirm more promptly.
8. Improve control of condition i.e. reduce fluctuation in drug level.
9. Improve bioavailability of same drugs.
10. Make use of special effects, e.g. sustained release aspect for morning relief of arthritis by dosing before bedtime.

1.3.2. Disadvantages of Sustained release drug delivery system: (*http: //www. pharmainfo.net)*

1. They are costly.
2. Unpredictable and often poor in-vitro in-vivo correlations, dose dumping, Reduced potential for dosage adjustment and increased potential first pass clearance.
3. Poor systemic availability in general.
4. Effective drug release period is influenced and limited by GI residence time.

1.3.3. Rationale of sustained release drug delivery system: *(Ansel H.C., 2009; Vyas S.P and Khar R.K., 2002)*

To optimizing the factor such as pharmacokinetic, pharmacodynamic and biopharmaceutical these are the rationale of sustained release dosage form, these properties of active ingredient in such a type its maximum reducing the adverse effect and controlling disease growth condition in short time period by loading less quantity of drug, when we are administered in the suitable route. Many drugs are longer action because half life and only need for once day dosing so these type of drug not for sustained or controlled release tablet to give therapeutic effect in blood and this nature of drug we can be manufacturing in immediate release tablet as like conventional

tablet. However, some drugs are not long action and need multiple daily dosing to obtain the therapeutic results.

Multiple daily dosing is inconvenient for the patient, chance of missed doses, made up doses and non compliance with the regimen. When the conventional tablet which may causes variation of plasma level peaks and valley associated with the using of each dose. However, when a dose should not be administering such a manner because the obtaining result like peaks and valley give the less action of therapy. For example if a dosage form is administered short time interval, minimum toxic concentration of drug may be reached, with toxic side effect can occur. If doses are missed or forgetted, the administered drug goes to sub therapeutic levels on those below the minimum effective concentration (MEC) may result, so there is no use to the patient.

1.3.4. Designing sustained-release drug delivery system: *(Shalin A. Modi, et al., 2011)*

Most of the orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety. It is assumed that increasing concentration at the absorption site will increase circulating blood levels, which in turn, promotes greater concentration of drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through biological milieu and absorption through an epithelial membrane to the blood. There are a variety of both

physicochemical and biological factors that come into play in the design of such system.

1.3.5. Factors Affecting Sustained Release Dosage Forms: (*Chein Y.W., 2009; http://www.pharmainfo.net)*

1.3.5.1. Physicochemical properties of drug:

a) Dose Size:

If an oral product has a dose size greater that 0.5gm it is a poor candidate for sustained release system, Since addition of sustaining dose and possibly the sustaining mechanism will, in most cases generates a substantial volume product that unacceptably large.

b) Aqueous Solubility:

Most of drugs are weak acids or bases, since the unchanged form of a drug preferentially permeates across lipid membranes drugs aqueous solubility will generally be decreased by conversion to an unchanged form for drugs with low water solubility will be difficult to incorporate into sustained release mechanism. The lower limit on solubility for such product has been reported 0.1mg/ml. drugs with great water solubility are equally difficult to incorporate in to sustained release system. pH dependent solubility, particularly in the physiological pH range, would be another problem because of the variation in pH throughout the GI tract and hence variation in dissolution rate.

c) Partition Coefficient:

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly compounds with relatively high partition coefficient are predominantly lipid soluble and consequently have very law

aqueous solubility. Compounds with very law partition coefficients will have difficulty in penetrating membranes resulting poor bioavailability.

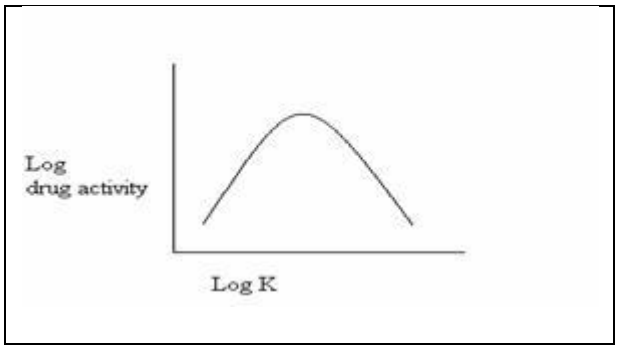


Figure 1.2: Typical relationship between drug activity and partition coefficient K.

d) Dissociation constant (pka):

The relationship between dissociation constant of compound and absorptive environment. Presenting drug in an unchanged form is adventitious for drug permeation but solubility decrease as the drug is in unchanged form.

e) Drug Stability:

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. Degradation will proceed at the reduced rate for drugs in the solid state, for drugs that are unstable in stomach, systems that prolong delivery ever the entire course of transit in GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered form a sustaining dosage from. This is because more drug is delivered in small intestine and hence subject to degradation.

f) Molecular size and diffusivity:

The ability of drug to diffuse through membrane it's so called diffusivity & diffusion coefficient is function of molecular size (or molecular weight). Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 to 10-9 cm^2 / sec. with values on the order of 10-8

being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 cm^2/sec. Thus high molecular weight drugs and / or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

g) Protein binding:

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are for the most part re-circulated and not eliminated, drug Protein binding can serve as a depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.

Extensive binding to plasma proteins will be evidenced by a long half life of elimination for drugs and such drugs generally most require a sustained release dosage form. However drugs that exhibit high degree of binding to plasma proteins also might bind to bio-polymers in GI tract which could have influence on sustained drug delivery. The presence of hydrophobic moiety on drug molecule also increases the binding potential.

1.3.5.2. Biological factors:

a) Biological Half Life:

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To action this, drug must enter in the circulation of approximately the same rate of which it is eliminated. The elimination rate is quantitatively described by half-life ($t_{1/2}$). Therapeutic compounds with short half lives are excellent candidates for sustained release preparations. Since this can reduce

dosing frequency. In general drugs with half-lives shorter than 3hrs are poor candidates of sustained release dosage forms of dose size will increase as well as compounds with long half lives, more than 8 hrs are also not used in sustained release forms because their effect is already sustained.

b) Absorption:

The rate, extent and uniformity of absorption of a drug are important factors when considered its formulation into a sustained release system. As the rate limiting step in drug delivery from a sustained-release system is its release from a dosage form, rather than absorption. Rapid rate of absorption of drug, relative to its release is essential if the system is to be successful. It we assume that transit time of drug must in the absorptive areas of the GI tract is about 8-12 hrs. The maximum half life for absorption should be approximately 3-4 hrs. Otherwise device will pass out of potential absorption regions before drug release is complete.

c) Distribution:

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. For design of sustained/ controlled release products, one must have information of disposition of drug.

d) Metabolism:

Drugs that are significantly metabolized before absorption, either in lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzymes systems are saturable. As drug is released at a slower rate to these regions less total drug is presented to the enzymatic. Process

device a specific period, allowing more complete conversion of the drug to its metabolite.

e) Side effects:

The incidence of side effect of a drug is depends on its therapeutic concentration level in blood. It can be remedy by the drug concentration level is controlled at which timing that drug exists in blood after administration. Toxic effect of a drug is expected above the maximum effective range level and fall in the therapeutic effect if a drug below the level of minimum effective range. So the above problem we can solve by making sustained release preparation.

f) Margin of safety:

Therapeutic index of a drug is very important for either sustained or controlled release delivery system. Its value only desired the margin of safety. Therapeutic index value it has been longer means excellent for preparation of sustained release tablet. Narrow therapeutic index of some drug precise to release the active content in therapeutic safe and effective range. Some drug like cardiac glycosides that therapeutic index value is very small, so it's not used for sustained release delivery system.

Therapeutic index = TD_{50} / ED_{50}

Where, TD_{50} - Median toxic dose

ED_{50} - Median effective dose.

1.4. Oral controlled and sustained release systems: (*Chein Y.W., 2009; http://www.pharmainfo.net; Shalin A. Modi, et al., 2011)*

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:

1.4.1. Continuous release systems:

These systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form. The various systems under this category are as follow,

A. Dissolution controlled release systems

B. Diffusion controlled release systems

C. Dissolution and diffusion controlled release systems

D. Ion exchange resin- drug complexes

E. pH dependent formulation

F. Osmotic pressure controlled systems

A. Dissolution controlled release systems:

These types of systems are easiest to design. The drug present in such system may be the one:

- With inherently slow dissolution rate e.g. Griseofulvin and Digoxin.
- That produces slow dissolving forms, when it comes in contact with GI fluids.
- Having high aqueous solubility and dissolution rate.

Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling their dissolution rate. Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by below equation.

$$Dm/dt = ADS/h$$

Where, S = Aqueous solubility of the drug.

A = Surface area of the dissolving particle or tablet.

D = Diffusivity of the drug and

h = Thickness of the boundary layer.

a) Matrix (or monolithic) dissolution controlled systems:

As the drug is homogeneously dispersed throughout the rate controlling medium, this system is also called as monolith system. It is very common and employs waxes such as bees wax, carnauba wax which control the drug release rate by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The drug release is often first order from such matrices.

b) Reservoir (Encapsulation) dissolution controlled systems:

In this type, the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose and polyethylene glycol. The dissolution rate of coat depends upon the solubility and thickness of the coating.

B. Diffusion controlled systems:

The basic mechanism of drug release from these two systems is fundamentally different besides these simple systems, combination of reservoir and monolithic systems also exist in practice. Diffusion systems are characterized by release rate of drug is dependent on its diffusion through inert water insoluble membrane barrier.

There are basically two types of diffusion devices.

a) Reservoir devices

b) Matrix devices

a) Reservoir Devices:

Reservoir Devices are those in which a core of drug is surrounded by polymeric membrane. The nature of membrane determines the rate of release of drug from system. The process of diffusion is generally described by a series of equations governed by Fick's first law of diffusion.

$$J = -D (DC/ DX)\ldots\ldots (1)$$

Where, 'J' is the flux of drug across the membrane given in units of amount / area time.

'D' is diffusion coefficient of drug in membrane in units of area / time. This is reflecting to drug molecule's ability to diffuse through the solvent and is dependent on the factors as molecular size and charge.

'dc/dt' represents rate of change in concentration C relative to a distance X in the membrane.

The law states that amount of drug passing across a unit area, is proportional to the concentration difference across that plane.

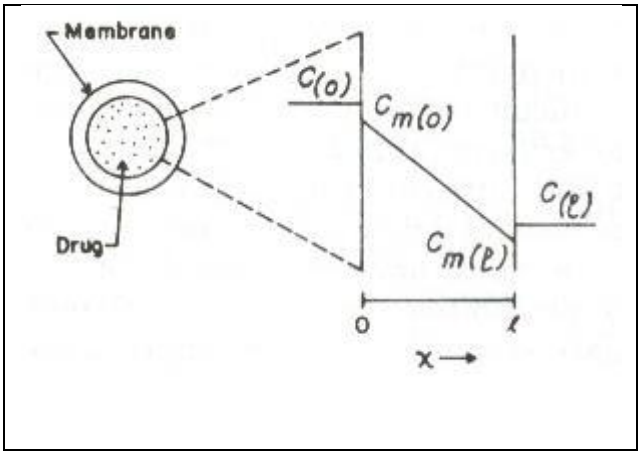


Figure 1.3: Schematic representation of reservoir diffusion device Cm (o), and Cm (d) represent concentration of drug inside surfaces of membrane and C (o) & C(d) represents concentration in adjacent regions.

If it is assumed that the drug on the both side of membrane is in equilibrium with its respective membrane surface which in equilibrium between the membrane surfaces and their bathing solutions as shown in Figure. Therefore the concentration just inside the membrane surface can be related to the concentration in the adjacent region by following expression.

$$K = Cm(o) / C(d) \quad \text{at } X = o \qquad (2)$$

$$K = Cm(d) / C(d) \quad \text{at } X = d \qquad (3)$$

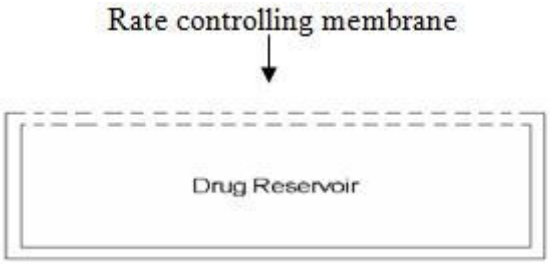
Where K = partition coefficient.

If we consider K & D are constants then equation (1) becomes,

$$J = D K \Delta C/d \qquad (4)$$

Where Δc is the concentration difference across the membrane and d is path length of diffusion. The simplest system to consider is that of slab, where drug release is from only one surface as shown Figure in this case equation (4) becomes

$$dMt/dt = ADK\Delta C/d \quad (5)$$



Non permeable polymer shell

Figure 1.4: Diagrammatic representation of slab configuration of reservoir diffusion system.

Where Mt = Mass of drug released after time t, dMt/dt. Steady state drug release rate of time‘t’; A= surface area of device.

In equation (7) if variables of right side of equation remain constant, then left side of equation represents release rate of system, a true controlled release system with a zero-order release rate.

A constant effective area of diffusion, diffusional path length, concentration difference, and diffusion coefficient are required to obtain a release rate that is constant. Reservoir diffusional systems have several advantages over conventional dosage forms. They can after zero order release of drug, kinetics of which can be controlled by changing the characteristics of the polymer to meet the particular drug and therapy conditions.

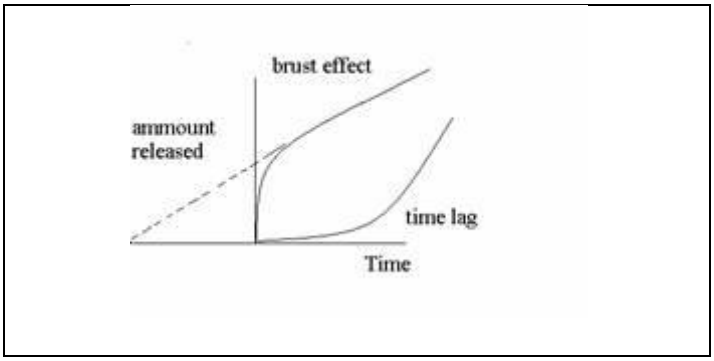


Figure 1.5: Plot showing approach to steady state for reservoir device that has been stored for an extended period (the burst effect curve) and for device that has been freshly made (the time lag curve).

Common methods used to develop reservoir type of devices include micro encapsulation of drug particles and press coating of tablets containing drug cores. In most cases particles coated by microencapsulation form a system where the drug is contained in the coating film as well as in the core of micro capsule. The drug release generally involves combination of dissolution and diffusion with dissolution being process that controls the release rate. If encapsulating material is selected properly will be the controlling process. Some materials such as membrane barrier coat alone or in combination, are hardened gelatin, methyl or methylcellulose, polyhydroxy methacrylate hydroxypropyl methylcellulose, polydroxy methacrylate, polyvinyl acetate & various waxes.

Matrix devices:

A matrix device, as the name implies, consists of drug dispersed homogenously throughout a polymer.

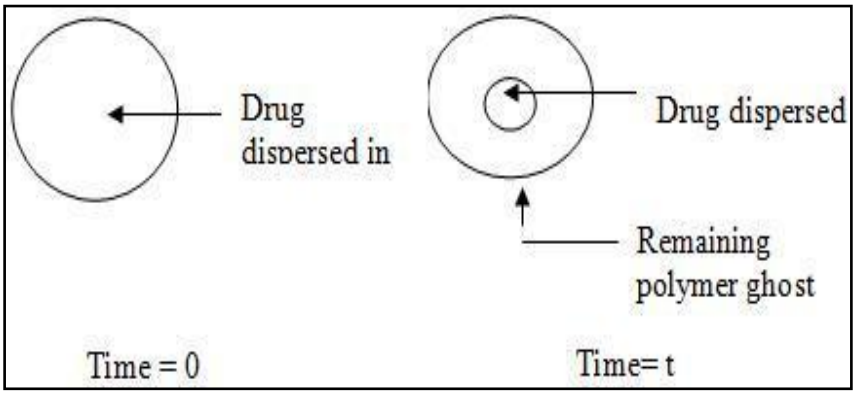


Figure 1.6: Matrix diffusion system before release (time=0) & after partial drug Release (time=t).

In this model drug in outside layer exposed to the bathing solution is dissolved first and diffused out of the matrix. This process continues with the interface between bathing solution and the solid drug moving controlled, the rate of dissolution of drug particles within the matrix must be faster that the diffusion rate of dissolved drug leaving matrix.

Following assumptions are made in retrieving the mathematical models are:

i. A pseudo steady state is maintained during drug release.

ii. The diameter of drug particles is less than the average distance of drug Diffusion through the matrix.

iii. The bathing solution provides sink conditions.

iv. The diffusion coefficient of drug in the matrix remains constant.

The next equation that describes the rate of release drugs dispersed in an inert matrix system has been derived by Higuchi.

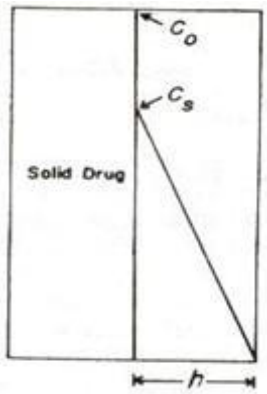


Figure 1.7: Schematic representation of the physical model used for a planer slab matrix diffusion device.

The change in amount of drug released per unit area dM and change in the thickness of the zone of the matrix that has been depleted of the drug,

$$dM/dh = Co\ dh - Cs\ /2 \qquad (6)$$

By Fick's first law,

$$dm = (Dm\ Cs/h)\ dt. \qquad (7)$$

where, Dm is diffusion coefficient in matrix if equation (6) & (7) are equated & solved for D that value of h sustituted back into the integrated form of equation (7) An equation for M is obtained.

$$M = [Cs\ Dm\ (2Co - Cs)\ t]\ ½ \qquad (8)$$

Similarly, a drug released from porous or granular matrix is described.

$$M = [Ds\ Ca\ (\epsilon/\tau)\ (2Co - \epsilon\ Ca)\ t]\ ½ \qquad (9)$$

Where, e = Porosity of matrix

τ = tortuosity.

Ca = Solubility of drug in release medium

Ds = diffusion coefficient of drug in release medium.

In this system drug is leached from matrix through channels or pores.

$$M = Kt^{1/2}$$

$$M = K \sqrt{t} \qquad (10)$$

Where K is constantan so, that plot amount of drug released verses square root of time should be linear if the release of drug from the matrix is diffusion controlled. The release rate of drug from such a device is not zero order, since if decreases with time but as previously mentioned, this may be clinically equivalent to constant drugs.

1.5. Matrix tablets: (*Chein Y.W., 2009; Harnish Patel, et al., 2011)*

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating SR dosage form.

Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems.

Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method

therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients.

Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

1.5.1. Advantages of matrix tablets:

- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Usage of less total drug.

- Improvement the bioavailability of some drugs.
- Improvement of the ability to provide special effects.

  Ex: Morning relief of arthritis through bed time dosing.

1.5.2. Disadvantages of matrix tablet:

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

1.5.3. Classification of matrix tablets:

1.5.3.1. On the Basis of Retardant Material Used:

Matrix tablets can be divided into 5 types.

1. Hydrophobic Matrices (Plastic matrices):

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet.

Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices

include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Lipid Matrices:

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with cetyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices:

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

The polymers used in the preparation of hydrophilic matrices are divided into three broad groups,

A. Cellulose derivatives:

Methylcellulose 400 and 4000Cps, Hydroxy ethylcellulose; Hydroxypropyl methylcellulose (HPMC) 25, 100, 4000 and 15000Cps; and Sodium carboxy methyl cellulose.

B. Non cellulose natural or semi synthetic polymers:

Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

Polymers of acrylic acid:

Carbopol-934, the most used variety.

4. Biodegradable Matrices:

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices:

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

1.5.3.2. On the Basis of Porosity of Matrix:

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified:

1. Macro porous Systems:

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2. Micro porous System:

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

3. Non-porous System:

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

1.5.4. Polymers used in matrix tablet:

Hydrogels:

Polyhydroxy ethyl methacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Poly acrylamide (PA).

Soluble polymers:

Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC).

Biodegradable polymers:

Polylactic acid (PLA), Polyglycolic acid (PGA), Poly caprolactone (PCL), Poly anhydrides, Poly orthoesters.

Non-biodegradable polymers:

Polyethylene vinyl acetate (PVA), Poly dimethyl siloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).

Mucoadhesive polymers:

Poly carbophil, Sodium carboxy methylcellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin.

Natural gums: Xanthan gum, Guar gum, Karaya gum, Locust bean gum.

1.5.5. Mechanism of drug release from matrix tablet:

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release,

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,

c) The bathing solution provides sink conditions at all times.

1.6. Methods used in tablet manufacturing: *(Lieberman H.A. and Lachman L., 1999; Ansel H.C., 2009; http://www.pharmainfo.net)*

Granulation:

Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates.

The reason for granulation:

- Become the pharmaceutical ingredient are free flowing
- Increase the denseness of ingredient
- We can formulate uniform granular size that does not existing apart
- Produce better compression characteristic of drug
- Controlling the rate of drug release from the dosage form
- Reduce dust in granulation technique
- The appearance of tablet can be achieved

Methods:

1. Direct compression
2. Wet granulation
3. Dry granulation

1.6.1. Direct compression:

In early days, most of the tablets require granulation of the powdered Active Pharmaceutical Ingredient (API) and Excipients. At the availability of new excipients or modified form of old excipients and the invention of new tablet machinery or modification of old tablet machinery provides an ease in manufacturing of tablets by simple procedure of direct compression.

Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression. Thus offering

advantage particularly in terms of speedy production. Because it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability.

1.6.1.1. Definition:

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.

1.6.1.2. The events that motivates the industry people to use direct compression technique:

I. Commercial availability of the directly compressible excipients possessing both good compressibility and good flowability. For example, Spray dried lactose, Anhydrous lactose, Starch-1500, microcrystalline cellulose, Di-Pac^{Ò}, sorbitol.

II. Major advances in tablet compression machinery:

i) Improved positive die feeding,

ii) Precompression of powder blend.

1.6.1.3 Merits:

i) Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.

ii) The most important advantage of direct compression is economical process. Reduced processing time, reduced labor costs, fewer manufacturing steps, and less number of equipments are required, less process validation, reduced consumption of power.

iii) Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive API's.

iv) Particle size uniformity.

v) Prime particle dissolution.

In case of directly compressed tablets after disintegration, each primary drug particle is liberated. While in the case of tablets prepared by compression of granules, small drug particles with a larger surface area adhere together into larger agglomerates; thus decreasing the surface area available for dissolution.

vi) The chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes is fewer.

vii) Chemical stability problems for API and excipient would be avoided.

viii) Provides stability against the effect of aging which affects the dissolution rates.

1.6.1.4. Merits over wet granulation process:

The variables faced in the processing of the granules can lead to significant tableting problems. Properties of granules formed can be affected by viscosity of granulating solution, the rate of addition of granulating solution, type of mixer used and duration of mixing, method and rate of dry and wet blending. The above variables can change the density and the particle size of the resulting granules and may have a major influence on fill weight and compaction qualities. Drying can lead to unblending as soluble API migrates to the surface of the drying granules.

1.6.1.5. Demerits:

Excipients Related:

i) Problems in the uniform distribution of low dose drugs.

ii) High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression.

iii) The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flow ability.

iv) Many active ingredients are not compressible either in crystalline or amorphous forms.

v) Direct compression blends may lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.

vi) Non-uniform distribution of colour, especially in tablets of deep colours.

Process Related:

i) Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression. When air is trapped, the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.

ii) In some cases require greater sophistication in blending and compression equipments.

iii) Direct compression equipments are expensive.

1.6.1.6. Manufacturing steps for direct compression:

Direct compression involves comparatively few steps:

- Milling of drug and excipients.
- Mixing of drug and excipients.
- Tablet compression.

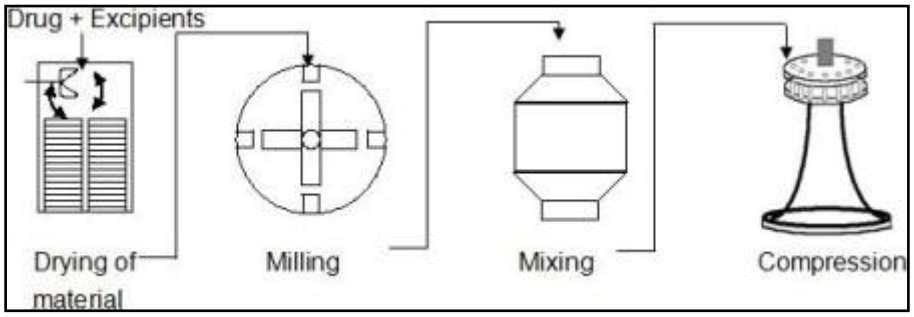


Figure 1.8: Manufacturing Steps for Direct Compression.

1.6.1.7. Direct compression Excipients:

Direct compression excipients mainly include diluents, binders and disintegrants. Generally these are common materials that have been modified during the chemical manufacturing process, in such a way to improve compressibility and flowability of the material.

The physicochemical properties of the ingredients such as particle size, flowability and moisture are critical in direct compression tableting. The success of direct compression formulation is highly dependent on functional behavior of excipients.

1.6.1.7.1. An ideal direct compression excipient should possess the following attributes:

i) It should have good compressibility.

ii) It should possess good hardness after compression, that is material should not possess any deformational properties; otherwise this may lead to capping and lamination of tablets.

iii) It should have good flowability.

iv) It should be physiologically inert.

v) It should be compatible with wide range of API.

vi) It should be stable to various environmental conditions (air, moisture, heat, etc.).

vii) It should not show any physical or chemical change in its properties on aging.

viii) It should have high dilution potential i.e. able to incorporate high amount of API.

ix) It should be colourless, odorless and tasteless.

x) It should accept colourants uniformity.

xi) It should possess suitable organoleptic properties according to formulation type, that is in case of chewable tablet diluent should have suitable taste and flavor. For example, mannitol produces cooling sensation in mouth and also sweet test.

xii) It should not interfere with bioavailability and biological activity of active ingredients.

xiii) It should be easily available and economical in cost.

Granulation method can be broadly classified into two types:

- Wet granulation and
- Dry granulation.

1.6.2. Wet granulation:

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

1.6.2.1. Important steps involved in the wet granulation:

i) Mixing of the drug(s) and excipients

ii) Preparation of binder solution

iii) Mixing of binder solution with powder mixture to form wet mass.

iv) Coarse screening of wet mass using a suitable sieve (6-12 # screens).

v) Drying of moist granules.

vi) Screening of dry granules through a suitable sieve (14-20 # screen).

vii) Mixing of screened granules with disintegrant, glidant, and lubricant.

1.6.2.2. Limitations of wet granulation:

i) The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.

ii) Loss of material during various stages of processing

iii) Stability may be major concern for moisture sensitive or thermo labile drugs

iv) Multiple processing steps add complexity and make validation and control difficult.

v) An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

1.6.3. Dry granulation:

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is pre-compressed and the resulting tablet or slug are milled to yield the granules.

The other method is to pre-compress the powder with pressure rolls using a machine such as Chilosonator.

1.6.3.1. Advantages:

The main advantages of dry granulation or slugging are that it uses less equipments and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

i) For moisture sensitive material

ii) For heat sensitive material

iii) For improved disintegration since powder particles are not bonded together by a binder

1.6.3.2. Disadvantages:

i) It requires a specialized heavy duty tablet press to form slug

ii) It does not permit uniform colour distribution

iii) Achieved with wet granulation where the dye can be incorporated into binder liquid.

iv) The process tends to create more dust than wet granulation, increasing the potential contamination.

1.7. DEPRESSION: *(http://www.about.com)*

Depression makes a person feel sad, hopeless, worthless, pessimistic and guilty. Often the sufferer has difficulty concentrating and making decisions, has a loss of appetite and weight or a weight gain, has difficulty sleeping, has a lack of energy and sometimes physical symptoms such as slow movement and speech. Depression must be taken seriously because of the high rate of suicide associated with it.

1.7.1. Most common types of depression

The following are descriptions of the most common types of depression.

1. Major Depressive Disorder

When people use the terms depression or clinical depression, they are generally referring to major depressive disorder. Major depressive disorder is a mood disorder characterized by a depressed mood, a lack of interest in activities normally

enjoyed, changes in weight and sleep, fatigue, feelings of worthlessness and guilt, difficulty concentrating and thoughts of death and suicide. If a person experiences the majority of these symptoms for longer than a two-week period, they may be diagnosed with major depressive disorder.

2. Dysthymic Disorder

Dysthymia (pronounced Dis-THIGH-me-uh) comes from the Greek roots dys, meaning "ill" or "bad," and thymia, meaning "mind" or "emotions." The terms dysthymia and dysthymic disorder refer to a mild to moderate, chronic state of depression.

3. Bipolar Disorder

Bipolar disorder is an illness that consists of alternating periods of elevated moods, called manic episodes, and depression. Mood swing run on a spectrum from mild mania (called hypomania) to more severe, debilitating highs. Periods of mania can last for hours, days, weeks or even months before depression returns.

4. Postpartum Depression

Pregnancy brings about many hormonal shifts. These dramatic shifts can sometimes affect mood. This is commonly known as the "baby blues." Postpartum depression can be more than just a case of the blues, however. It can range from mild symptoms that go away without treatment all the way up to postpartum psychosis, which left untreated, may be responsible for tragic murders of children.

5. Seasonal Affective Disorder

If you experience depression, sleepiness, weight gain and carbohydrate cravings during the winter months, but feel great as soon as spring returns, you may have a condition called Seasonal Affective Disorder (SAD).

6. Premenstrual Dysphoric Disorder

The most frequently reported symptoms of premenstrual syndrome (PMS) include irritability, fatigue, anxiety, nervous tension, mood swings, depression, feeling overwhelmed or out of control, physical symptoms of swelling or bloating of the abdomen or extremities, appetite changes and food cravings, aches, and breast tenderness. These symptoms may occur for several days to 2 weeks before menses but subside with the onset of the menstrual period. When these symptoms, especially those of mood, are severe, a diagnosis of premenstrual dysphoric disorder (PMDD) may be made.

7. Atypical Depression

Do you experience symptoms such as improved mood when good things happen, overeating, sleeping too much or sensitivity to rejection? These are symptoms characteristic of atypical depression, which is a type of depression which does not follow the "typical" set of depression symptoms, such as a lack of appetite and insomnia. It is actually more common than the name might imply.

1.7.2. Etiology of depressions

Though there are several theories about what cause classical depressions, 5-HT plays an important role in the genesis of depressive psychosis as evidenced by increasing in 5-HT (or) its precursors in the brain in patients of depressive psychosis. Many drugs (antidepressants) based on 5-HT metabolization and activations are now available. They prevent the uptake of 5-HT from serotonergic nerve endings, thereby increasing endogeneous 5-HT levels.

Similarly, noradrenaline (NAD) also plays an important role in the genesis of depression as its absence in various areas of the CNS leads to the development of

depressions. Antidepressant like MAO and SNRI act by inhibiting the metabolism of NAD (or) preventing its reuptake into the adrenergic nerve ending.

1.7.3. Symptoms and Signs of Depression

Depression is not something you feel for a day or two before feeling better. In true depressive illnesses, the symptoms last weeks, months, or sometimes years if you don't seek treatment. If you are depressed, you are often unable to perform daily activities. You may not care enough to get out of bed or get dressed, much less work, do errands, or socialize.

Adults: You may be said to be suffering from a major depressive episode if you have a depressed mood for at least two weeks and have at least five of the following clinical symptoms:

- Feeling sad or blue
- Crying spells
- Loss of interest or pleasure in usual activities
- Significant increase or decrease in appetite
- Significant weight loss or weight gain
- Change in sleep pattern: inability to sleep or excessive sleeping
- Agitation or irritability
- Fatigue or loss of energy
- A tendency to isolate from friends and family
- Trouble concentrating
- Feelings of worthlessness or excessive guilt
- Thoughts of death or suicide

1.7.4. Facts/Statistics of Depression

Depression affects about 19 million Americans annually. It is estimated to contribute to half of all suicides. About 5%-10% of women and 2%-5% of men will experience at least one major depressive episode during their adult life. Depression affects people of genders, as well as all races, incomes, ages, and ethnic and religious backgrounds. However, it is twice as common in women compared to men and three to five times more common in the elderly than in young people

1.7.5. Diagnosis of Depression

Many providers of health care may help diagnose clinical depression: licensed mental-health therapists, family physicians, or other primary-care providers, specialists whom you see for a medical condition, emergency physicians, psychiatrists, psychologists, psychiatric nurses, and social workers.

If one of these professionals suspects that you have depression, you will undergo an extensive medical interview and physical examination. As part of this examination, you may be asked a series of questions from a standardized questionnaire or self-test to help assess your risk of depression and suicide.

Depression may be associated with a number of other medical conditions or can be a side effect of various medications. For this reason, routine laboratory tests are often performed during the initial evaluation to rule out other causes of your symptoms. Occasionally, an X-ray, scan, or other imaging study may be needed

1.7.6. Treatment of Depression

If your symptoms indicate that you have clinical depression, your health-care provider will strongly recommend treatment. Treatment may include addressing any

medical conditions that cause or worsen depression. For example, an individual who is found to have low levels of thyroid hormone might receive thyroid hormone replacement with levothyroxine (Synthroid, Levoxyl). Other components of treatment may be supportive therapy, such as changes in lifestyle and behavior, psychotherapy, complementary therapies, and may often include medication. If your symptoms of depression are severe enough to warrant treatment with medication, you are most likely to feel better faster and for longer when medication treatment is combined with psychotherapy.

Most practitioners will continue treatment of major depression for six months to a year. Treatment for teens with depression can have a significantly positive effect on the adolescent's functioning with peers, family, and at school. Without treatment, your symptoms will last much longer and may never get better. In fact, they may get worse. With treatment, your chances of recovery are quite good.

1.7.7. Prevention of Depression

People who have risk factors for depression should be "screened" regularly by their health-care provider. This means that when they see their health-care provider, questions should be asked that might indicate depression.

If identified early, those who are at risk for depression are more likely to benefit from treatment.

NEED

AND

OBJECTIVES

2. NEED AND OBJECTIVES

Need of this work are:

- Venlafaxine Hydrochloride is the most widely used anti- depressant agent in the treatment of major depression disease has a low bioavailability, because of its poor absorption. It undergoes hepatic metabolism and its mean elimination half life (5 hours) drug requires frequent dosing by oral route, of various recent techniques for controlling drug release, matrix system offer various advantages of ease of formulation better control on release profile of drug and better patient compliance.
- The pronounced fluctuation resulting from the conventional drug administration are likely to yield period of therapeutic effects when the concentration falls below the minimum therapeutic drug concentration and can be controlled within the narrow therapeutic range by use of sustained release system. Which will minimize the severity of side effects.
- Hydrophobic polymer matrix system are widely used for designing oral sustained release drug delivery dosage form because of their flexibility to provide a desirable drug release profile, cost effectiveness and broad regulatory acceptance.
- Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The matrix tablets formulation by wet granulation method is most acceptable in large scale production.

Objectives of the work are:

- To evaluate the physical characters of prepared sustained release tablets
- To elucidate the effect of polymer composition, on the release kinetics and
- To determine the chemical compatibility of formulation containing various ratios of polymer and drug.

Conventional oral formulations of Venlafaxine Hydrochloride are administered multiple times a day (75 to 225 mg) because of its moderate half-life ($t_{1/2}$ = 5 hours).

Treatment of Depression using conventional formulations of Venlafaxine Hydrochloride is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multi-dose therapy, poor patient compliance, and high cost. Sustained release once-daily formulations of Venlafaxine Hydrochloride can overcome some of these problems.

PLAN OF WORK

3. PLAN OF WORK

The present work was carried out to design and evaluate sustained-release tablets of Venlafaxine Hydrochloride, an antidepressant drug. The sustained-release matrix tablets were prepared by Hot melt granulation using carnauba wax, cetyl alcohol, stearic acid, lactose, and talc keeping in view the objectives described above the following plan of work was adopted.

THE SCHEME OF THE ENTIRE WORK IS LISTED AS FOLLOWS:

- Literature review
- Selection of drug and excipients
- Procurement of drug and excipients
- Physicochemical studies (organoleptic properties, melting point and solubility)
- Standardization of the method and construction of calibration curve for the estimation of Venlafaxine Hydrochloride, quantification of drug.
- Compatibility studies of drug and polymer by FTIR spectral and DSC studies
- Formulation of Venlafaxine Hydrochloride sustained release matrix tablets by using polymers like carnauba wax, cetyl alcohol and stearic acid by Hot melt granulation method.

- Evaluation of prepared granules (pre-compression parameters)
    i. Angle of repose
    ii. Determination of bulk density
    iii. Determination of tapped density
    iv. Compressibility index
    v. Hausner ratio
- Evaluation of physical parameters of Venlafaxine sustained-release tablets (post-compression parameters)
    i. Thickness and diameter
    ii. Hardness
    iii. Friability
    iv. Weight variation
    v. Drug content
- Evaluation of *in vitro* release characteristics of all formulations by using USP dissolution apparatus type I (Basket).
- To study the mechanism of drug release by applying kinetic parameters.
- To perform stability studies as per ICH guidelines.

LITERATURE REVIEW

4. LITERATURE REVIEW

Amelia Avachat., ***et al.*** **(2007)** was developed and characterized an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulfate (CS). A hydrophilic matrix-based tablet using different concentrations of hydroxypropyl methylcellulose (HPMC) was developed using wet granulation technique to contain 100 mg of DS and 400 mg of CS. Formulations prepared were evaluated for the release of DS and CS over a period of 9 hours in pH 6.8 phosphate buffer using United States Pharmacopoeia (USP) type II dissolution apparatus. Along with usual physical properties, the dynamics of water uptake and erosion degree of tablets were also investigated. The in vitro drug release study revealed that HPMC K100 CR at a concentration of 40% of the dosage form weight was able to control the simultaneous release of both DS and CS for 9 hours. The release of DS matched with the marketed CR tablet of DS with similarity factor (f2) above 50.

Deepak S., ***et al.*** **(2010)** had developed sustained release formulation of quetiapine fumarate using HPMC and PVP K30. The study involves fixing the drug and polymer ratio for control the drug release up to the desired time. The effect of polymer concentration and polymer blend concentration were also studied. Dissolution studies were performed in 0.1N HCl for 2 hrs and in phosphate buffer up to 12 hours. From the release it was observed that the polymer blend of HPMC/PVP K30 were successfully sustained the release of drug up to 12 hrs.

Gohel M.C., *et al.* (2007) was developed modified release of isoniazid using hydroxypropyl methylcellulose as a rate controlling agent. The low viscosity grade hydroxypropyl methylcellulose, medium viscosity grade hydroxypropyl methylcellulose and high viscosity grade Hydroxypropyl methylcellulose were used to prepare the matrix tablets. The tablets, prepared by direct compression, were subjected to physical characterization and *in-vitro* drug release studies. The release rate was strongly influenced by the type of polymer and concentration of polymer.

Harris Shoaib M., *et al.* (2006) had formulated a once daily sustained release matrix tablet of ibuprofen using HPMC as release controlling factor and to evaluate drug release parameters as per various release kinetic models. The tablets were directly compressed using Avicel pH 101 and magnesium stearate. Different dissolution models were applied to drug release data in order to evaluate release mechanism. The drug release data fit well to the Higuchi expression.

Indranil Kumar Yadav., *et al*. (2010) was developed the oral sustained release matrix tablets of aceclofenac using hydrophilic and hydrophobic polymers. Aceclofenac is a non steroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis and its biological half life is 4hrs. Controlled release formulations of aceclofenac (200 mg) were prepared by direct compression method. The tablets were subjected to physicochemical, in-vitro drug release and stability studies. The drug release from optimized formulations F1, F4 and F7 was extended for a period of 12 hrs. The optimized formulations were subjected to stability studies for three months at 45°C temperature with RH 75±5%, and showed stability with respect to physicochemical

parameters and release pattern. Results of the present study indicated the suitability of hydrophilic and hydrophobic polymers in the preparation of matrix based sustained release formulation of aceclofenac.

Kalyani C., *et al.* (2009) had designed oral sustained matrix tablets of zidovudine using HPMC K4M, guar gum and ethyl cellulose as the retardant polymers. Factors like polymer proportion, polymer type and effect of filler type on the in vitro release of the drug. The formulations were prepared by wet granulation technique. The granules were evaluated and all formulations showed compliance with pharmacopoeial standards. Formulation F2 and F8 sustained the release for 12 hrs. Formulation F5 was found to be best which contains 15% HPMC using MCC as diluent release 10 hours only.

Madhusmruti K., *et al.* (2010) was developed sustain release matrix formulation of Propanolol hydrochloride and investigate the effects of both hydrophilic and hydrophobic polymer on *in-vitro* drug release. Matrix tablets were prepared by direct compression method using different concentrations of Hydroxypropyl methyl cellulose (HPMC) and Ethyl Cellulose (EC). Prepared formulations were subjected to various studies like hardness, friability, thickness, % drug content, weight variation, dynamic of water uptake and erosion etc. Tablets were subjected to *in-vitro* drug release in 0.1N HCl (pH 1.2) for first 2 hours followed by phosphate buffer (pH 6.8) remaining time.

Patil U.K., *et al.* (2008) prepared and evaluated sustained release matrix tablet using natural polymers like pectin, guar gum and xanthan gum. Furosemide is

used as the model drug and the formulations were compressed by a direct compression. The tablets were evaluated for physical characteristic and all the formulations were found to be in acceptable limits. Among the polymers guar gum was found to exhibit greater swelling index than pectin and xanthan gum.

Prabu Moses., ***et al.*** **(2010)** had formulated Ciprofloxacin controlled release matrix tablets using HPMC K100M, Guar gum, Carboxy methylcellulose, starch, polyvinyl pyrrolidone k30, magnesium stearate, isopropyl alcohol. Formulated tablets were taken to evaluation studies such as hardness, weight variation, friability, drug content and thickness.

Potu Apparao., ***et al.*** **(2011)** had formulated and evaluated gum based sustained release matrix tablets of Lamivudine using different natural polymers such as Guar gum, Xanthan gum, Rosin gum, Pectin, and Sodium alginate taken at 30%, 40% and 50% of the total weight of the tablet. Lamivudine is a potent hydrophilic anti viral agent indicated for treatment of AIDS (Acquired Immunodeficiency Syndrome). All the formulations were able to retard the release of the drug beyond 18 hours except pectin and sodium alginate were unable to sustain the drug release from the matrix tablets. F5 (40% Xanthan Gum) formulation was selected as optimized formulation.

Raghuram Reddy K., ***et al.*** **(2003)** had formulated once daily sustained release matrix tablets of nicorandil, a novel potassium channel openers used in the treatment of cardiovascular disease. The tablets are prepared by wet granulation technique using ethanolic solutions of ethylcellulose (EC), Eudragit RL-100, Eudragit

RS-100, and polyvinyl pyrrolidone as granulating agents with hydrophilic matrix materials such as HPMC, sodium carboxylic cellulose and sodium alginate. The granules were studied for physiochemical characteristics and for evaluation parameters. Granules showed good flow property and tablet formulations are all within official limits. From the dissolution studies the formulation F1 could extend the release for 24 hrs and thus it exhibited the most successful formulation of the study.

Raju Manda., ***et al.*** **(2010)** was developed a sustained release matrix tablet of aceclofenac using different natural polymers (Guar gum, Xanthan gum, Chitosan) in various proportions as release controlling factor by direct compression method. The *in vitro* dissolution study was carried out for 11 hours using United States Pharmacopoeia (USP) 1 Basket-type dissolution apparatus in 0.1N hydrochloric acid for first 2 hours and phosphate buffer pH 7.4 for 9 hours. The in vitro release study shows that only F9 formulation was releases the drug in a sustained manner for 11 hours. This study explored the optimum concentration and effect of polymer(s) on acelofenac release pattern from the tablet matrix for 11 hour period.

Saleh M. Saidan, ***et al.*** **(2005)** developed guar gum matrix tablets for oral controlled release of water-soluble Diltiazem hydrochloride prepared by using microcrystalline cellulose, starch, magnesium stearate and talc. In vitro drug release studies were performed using USP dissolution rate apparatus.

Sandip B. Tiwari., ***et al.*** **(2003)** had formulated Tramadol hydrochloride using hydrophilic and hydrophobic matrix system for controlled release. The effect of

concentration of hydrophilic and hydrophobic polymers on the release rate of Tramadol was studied. Hydrophilic matrix tablets prepared by wet granulation technique, while hydrophobic matrix tablets prepared by melt granulation technique. In vitro dissolution studies were performed.

Saravanabhavan Shanmugam., ***et al*****. (2010)** was developed sustained release matrix tablets of aceclofenac. The tablets were prepared with different ratios of hydroxypropyl methylcellulose K100M and ethylcellulose by wet granulation technique. The solubility study of the aceclofenac was conducted to select a suitable dissolution medium for in vitro drug release studies. In vitro dissolution study was carried out for all the formulation and the results compared with marketed sustained release tablets**.** The drug release from matrix tablets was found to decrease with increase in polymer ratio of hydroxypropyl methylcellulose as well as ethylcellulose. Formulation F3 exhibited almost similar drug release profile in different dissolution media as that of marketed tablets.

Seema Pushkar., ***et al.*** **(2009)** was developed the extended release tableted matrix devices for once daily dosing of diclofenac sodium, and their evaluation for performance and compliance with official pharmacopoeial and allied pharmaceutical requirements. The matrix tablets were prepared by drug incorporated polymer matrix, formulated using different combinations and ratios of hydroxypropyl methylcellulose (HPMC), sodium carboxy methylcellulose (Sodium CMC), and sodium alginate (NaAlg). Several preformulation trials were conducted to study the effect and optimization of various formulation and process parameters. The drug loaded polymeric matrices so prepared were compressed to tablets and studied for drug the

release behaviour and comparative kinetic characterization along with six popular marketed brands of Diclofenac SR tablets. The formulated granules and tablets compressed complied with compendial and mechanistic requirements. The *in vitro* results shown a better release profile of formulated delivery system when compared to marketed brands extended up to 24 hours. The various formulations have shown an extended release up to 11 – 23 hours in different release environments.

Sundaramoorthy K., *et al*. (2011) had formulated monolithic matrix tablets of metformin hydrochloride as extended release tablets by employing ethyl cellulose polymer and the extended release characterization of the formulated tablets was investigated. Extended release matrix tablets containing 500 mg metformin hydrochloride were developed by changing concentration of drug: polymer (EC) in the ratio of 5:1, 5:2, 5:3 and 5:4 by direct compression. Formulations were optimized based on the acceptable tablet properties *in-vitro* and *in-vivo* drug release. The result of *in-vitro* and *in-vivo* drug release studies indicated that formulation (drug: polymer =5:3), was the most successful of the study and exhibited constant and extended release of metformin hydrochloride 99-100.5% release at the end of 10 hours compared with reference standard. A decrease in release of the drug was observed on increasing polymer ratio at certain level. The $t_{25\%}$, $t_{50\%}$ and $t_{90\%}$ drug release values were calculated from selected formulation F3 on every specified period of stability studies and comparison of both room and accelerated condition by statistical t-test, there was no difference between storage temperature. The formulation F3 was showed similar *in-vitro* and *in-vivo* drug release when compared to market sustained release tablet (F5M).

Literature review indicating work carried out on selected drug Venlafaxine Hydrochloride is given below:

Radhika P R., *et al.* (2011) was developed sustained release matrix tablets of Venlafaxine Hydrochloride using a high permeable Eudragit RLPO and low permeable Eudragit RSPO in different ratios. Tablet matrices were prepared by direct compressionand were formulated as F1 ,F2 and F3 by using the above mentioned polymers. Technological characterizations like thickness, diameter, weight variation test, drug content, hardness, and friability were carried out with the formulated matrix tablet .The in-vitro drug releases of the formulated tablets were measured using the USP -24 types II dissolution apparatus. The formulations showed an optimum hardness, constant weight uniformity and low friability. The kinetic release treatment showed that the release of drug follows Zero order kinetic (r2 =0.9965), Koresmeyer equation gave value of r2= 0.9980 which was close to one indicating that the drug was released by Zero order kinetic. The in-vitro drug release data to Koresmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release. The formulation F1 containing high quantity of Eudragit RSPO provided the slowest release profile and 90 % of the drug content was released after 18 hours than other formulations. The systematic formulation approach enabled to develop sustained release Venlafaxine Hydrochloride tablets. Further investigations are needed to confirm the in vivo efficacy and this study demonstrated that Eudragit polymer can provide controlled release.

Mukesh C. Gohel., *et al*. (2009) was developed venlafaxine hydrochloride-Layered tablets for obtaining sustained drug release. The tablets containing

Venlafaxine hydrochloride 150 mg were prepared by wet granulation technique Using xanthan gum in the middle layer and barrier layers. The granules and tablets were characterized. The *in vitro* drug dissolution study was conducted in distilled water. The tablets containing two lower strengths were also developed using the same percentage composition of the middle layer. Kinetics of drug release was studied. The optimized batches were tested for water uptake study. Radar diagrams are provided to compare the performance of formulated tablets with the reference products, Effexor XR capsules. The granules ready for compression exhibited good flow and compressibility when xanthan gum was used in the intragranular and extragranular fractions. Monolayer tablets failed to give the release pattern similar to that of the reference product. The drug release was best explained by Weibull model. A unified Weibull equation was evolved to express drug release from the formulated tablets. Lactose facilitated drug release from barrier layers. Substantial water uptake and gelling of xanthan gum appears to be responsible for sustained drug release. The present study underlines the importance of formulation factors in achieving same drug release pattern from three strengths of venlafaxine hydrochloride tablets.

Nikil Karani A., *et al.*, (2009) have reported new, simple and cost effective uv-spectrophotometric method was developed for the estimation of venlafaxine hydrochloride in bulk and pharmaceutical formulation venlafaxine hydrochloride was estimated at 225.27 nm in distilled water. Linearity range was found to be $3.4x10^4$ mol^{-1} cm in distilled water. These methods were tested and validated for various parameters according to ICH guidelines and USP. The results demonstrated that the procedure is accurate, precise and reproducible while being simple, cheap and less time consuming and can be suitably applied for the estimation of venlafaxine hydrochloride in different dosage form and dissolution studies.

Vimala Shirvi D., *et al.*, (2010) have developed for the estimation of venlafaxine hydrochloride in raw material and pharmaceutical dosage form. In this method venlafaxine hydrochloride showed zero crossing at 274 nm, with a sharp peak at 285 nm. Beers law was obeyed in the concentration range of 40-120 µg/ml. The limit of detection and limit of quantification were found to be 1.82µg/ml and 5.49µg/ml respectively. The method was successfully applied to the determined of venlafaxine hydrochloride in tablet.

K. Sreenivasa rao., *et al.* (2011) had formulated SRmatrix tablet using hydrophilic polymer such as HPMC, Eudragit RS100, and Ethyl cellulose as releases retardants. All the precompressional parameters were found to be within the standard limits. Tablets were evaluated for hardness, friability, thickness, drug content, in Vitro release, swelling and stability studies. The effect of polymer concentration binary polymer mixture and wet granulation method on drug release profile was studied. It was absorbed that the type of polymer and its concentration has influence the drug release from matrix tablet. Matrix tablet content a blend of HPMC and ethyl cellulose successfully sustained the release of Venlafaxine for a period of 17hr. Precompressional parameter indicated that granules used preparing tablets with free flowing. Post-compressional parameters were withinthe acceptable limit. The concentration of Venlafaxine was kept constant, lactose used as filler.The sustained release fromethyl cellulose and HPMC was due to interaction between ethylcellulose chain ionic polymer and HPMC chain, non-ionic polymer, which resulted in favorable increase in the water uptake capacity and gel viscosity, leading to better controlover the release of Venlafaxine F4 showed the sustained release of Venlafaxine as desired. The study revealed that the ethyl cellulose and HPMC can be used for the formulation of sustained release matrix tablet of Venlafaxine.

Atul A. Bodkhe., ***et al.*** **(2010)** had formulated with Venlafaxine Hydrochloride equivalent to 37.5 mg of Venlafaxine base. Matrix system based on non swellable polymers was selected for sustaining the drug release. Different polymers and waxes viz. HPMC, stearic acid, cetyl alcohol, ethyl cellulose etc. were studied. Combinations of non swellable waxes with HPMC were also tried in order to get the desired sustained release profile over a period of 24 hours. The effect of drug to wax ratio on in-vitro release was studied.

Bhalekar., ***et al.*** **(2008)** had formulated a sustained drug delivery system of Venlafaxine Hydrochloride by using a wax matrix system. The effects of bees wax and carnauba wax on drug release profile was investigated. A 3^2 full factorial design was applied to systemically optimize the drug release profile. Amounts of carnauba wax (X_1) and bees wax (X_2) were selected as independent variables and release after 12 hours and time required for 50% drug release were selected as dependent variables. A mathematical model was generated for each response parameter. Both waxes retarded release after 12 hours and increases the t_{50} but bees wax showed significant influence. The drug release pattern for all the formulation combinations was found to be approaching Peppas kinetic model. Suitable combination of two waxes provided fairly good related release profile. The response surfaces and contour plots for each response parameter are presented for further interpretation of the results. The optimum formulations were chosen and their predicted results found to be in close agreement with experimental findings.

S Bagdiya Om prakash., ***et al.*** **(2011)** had developed the extended release formulation of Venlafaxine that releasesthe drug and maintian the plasma drug concentration for more than12h. Polymers like Hydroxypropylmethylcellulose (HPMC) K4M and K00M, NovocoatK100M, xanthan gum, Polyox, Carbopol etc. Weres elected for sustaining the drug release. The tablets were prepared by direct compression method. In vitro drug release study revealed that Novocoat 100 Malone was not able to retard the drug release whereas carobopol has High potential to retard the drug release due to its gelling property. Kinetic modeling of in vitro drug release data was best fitted in Korsmeyer-Peppas equation indicates drug releases by mixed mechanism of diffusion and erosion. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines.

DRUG AND EXCIPIENTS PROFILE

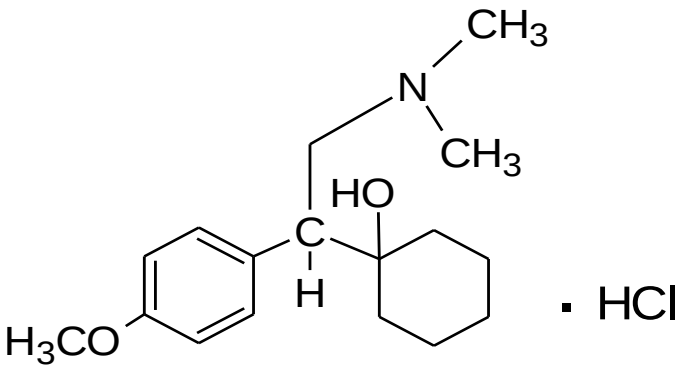
5. DRUG AND EXCIPIENTS PROFILE

5.1. Drug profile:

Venlafaxine Hydrochloride: *(The Merck Index)*

Chemical name : Dimethyl {5-[2-(1-methylamino-2nitrovinylamino) ethylthiomethyl] furfuryl}-amine hydrochloride.

Structural formula :



Molecular formula : $C_{13}H_{27}NO_2$, HCl

Molecular weight : 313.86

Melting point : 215-217°C

Drug content : 99-101%

Physicochemical properties: *(www.Chemicalbook.com)*

Description : White or almost white powder.

Solubility **:** Freely soluble in water and methanol, insoluble (or) slightly soluble in acetone.

Category **:** serotonin-norepinephrine reuptake inhibitor(SNRI) class

Dose **:** 75-225 mg/day (divided in 2-4 doses)

Pharmacology: *(www.About CNSforum.com/venlafaxine)*

Venlafaxine is a unique antidepressant, and is usually categorized as a serotonin-norepinephrine reuptake inhibitor (SNRI), but it has been referred to as a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI). Depression is associated with reduced levels of the monoamines in the brain, such as 5-HT. The selective 5-HT and noradrenaline re-uptake inhibitors (SNRIs) are thought to restore the levels of 5-HT and noradrenaline in the synaptic cleft by binding at their re-uptake transporters preventing the re-uptake and subsequent degradation of 5-HT and noradrenaline. This re-uptake blockade leads to the accumulation of monoamines in the synaptic cleft and the concentration returns to within the normal range. This action of SNRIs is though to contribute to the alleviation of the symptoms of depression. In the presence of the SNRIs, small amounts of 5-HT and noradrenaline continue to be degraded in the synaptic cleft.

Pharmacokinetics: (*Goodman and Gilman, 2006)*

Absorption **:** Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite.

Volume of distribution **:** 7.5±3.7 L/kg

Partition coefficient **:** octanol/water- 0.43

Oral bioavailability **:** 10-45%

Plasma half life **:** 5hrs.

Plasma protein binding **:** 27%

Indications: *(Tripathy K.D., 2008)*

- In endogeneous (major) depression.
- Obsessive-compulsive and phobic states
- Anxiety disorder
- Neuropathic pain
- Attention deficit-hyperactive disorder in children
- Enuresis
- Migraine
- Pruritus.

Adverse Effect: *(www.drugbank.ca)*

Venlafaxine hydrochloride is generally well tolerated, with a low incidence of adverse effects. The most common side effects of venlafaxine are nausea, somnolence, headache, dry mouth, sweating, hypotension, nervousness and abnormal ejaculation, dizziness, insomnia, sedation and constipation. At high doses, there may be an increase in blood pressure.

Drug Interaction:

Venlafaxine should not be used with MAOIs and at least 14 days should elapse between stopping an MAOI and starting treatment with venlafaxine. Although the synergistic effects may not be as bad as with other antidepressants, it is still not recommended to take venlafaxine with alcohol. Venlafaxine may lower the seizure threshold, and co administration with other drugs that lower the seizure threshold such as bupropion and tramadol should be done with caution and at low doses. Although cimetidine inhibits the hepatic metabolism of venlafaxine, it has no effect on the active metabolite of venlafaxine, o-desmethylvenlafaxine

Dosage Forms: *(http://en.wikipedia.org/wiki/Venlafaxine)*

- Tablets : 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg and 225mg.
- Tablet : ER- 37.5 mg, 75 mg, and 150 mg and 225mg.
- Capsules ER : 7.5 mg (gray/peach), 75 mg (peach), and 150 mg (brownish red).

Contraindications:

Venlafaxine is not recommended in patient with hypersensitive, Glaucoma, Pregnant women, Heart disease and hypertension. It should never be used with a monoamine oxidase inhibitor (MAOI), as it can cause potentially fatal serotonin syndrome. Caution should also be used in those with a seizure disorder.

5.2. Excipients profile:

5.2.1. Carnauba wax: ***(****Raymond C. R., et al., 2009)*

Nonproprietary names:

BP : Carnauba Wax

JP : Carnauba Wax

PhEur : Carnauba Wax

USP-NF : Carnauba Wax

Synonyms:

Brazil wax; caranda wax; cera carnauba.

Chemical name and CAS registry number:

Carnauba wax [8015-86-9]

Functional category:

Coating agent.

Applications in pharmaceutical formulation or technology:

Carnauba wax is widely used in cosmetics, certain foods, and Pharmaceutical formulations. Cosmetically, carnauba wax is commonly used in lip balms.

Carnauba wax is the hardest and highest-melting of the waxes commonly used in pharmaceutical formulations and is used primarily as a 10% w/v aqueous emulsion to polish sugar-coated tablets. Aqueous emulsions may

be prepared by mixing carnauba wax with an ethanolamine compound and oleic acid. The carnauba wax coating produces tablets of good luster without rubbing. Carnauba wax may also be used in powder form to polish sugarcoated tablets.

Carnauba wax (10–50% w/w) is also used alone or with other excipients such as hypromellose, hydroxypropyl cellulose, alginate/ pectin-gelatin, Eudragit, and stearyl alcohol to produce sustained release solid-dosage formulations.

Carnauba wax has been experimentally investigated for use in producing microparticles in a novel hot air coating (HAC) process developed as an alternative to conventional spray-congealing techniques. In addition, carnauba wax has been used to produce gel beads for intragastric floating drug delivery and has been investigated for use in nanoparticulate sunscreen formulations.

Description:

Carnauba wax occurs as a light brown - to pale yellow – colored powder, flakes, or irregular lumps of a hard, brittle wax. It has a characteristic bland odor and practically no taste. It is free from rancidity. Various types and grades are available commercially.

Melting point:

80–88°C

Solubility:

Soluble in warm chloroform and in warm toluene; slightly soluble in boiling ethanol (95%); practically insoluble in water

Stability and storage conditions:

Carnauba wax is stable and should be stored in a well-closed container, in a cool, dry place.

5.2.2. Cetyl alcohol: ***(****Raymond C. R., et al., 2009)*

Nonproprietary names:

BP : Cetyl Alcohol

JP : Cetanol

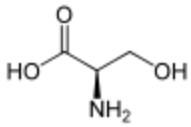
PhEur : Cetyl Alcohol

USP-NF : Cetyl Alcohol

Synonyms:

Alcohol cetylicus; Avol; Cachalot; Crodacol C70; Crodacol C90; Crodacol C95; ethal; ethol; HallStar CO-1695; 1-hexadecanol; nhexadecyl alcohol; Hyfatol 16-95; Hyfatol 16-98; Kessco CA; Lanette 16; Lipocol C; Nacol 16-95; palmityl alcohol; Rita CA; Speziol C16 Pharma; Tego Alkanol 16; Vegarol 1695.

Structural formula:



Chemical name and CAS registry number:

Hexadecan-1-ol [36653-82-4]

Description:

Cetyl alcohol occurs as waxy, white flakes, granules, cubes, or castings. It has a faint characteristic odor and bland taste.

Melting point:

45-52°C

Empirical formula and molecular weight:

$C_{16}H_{34}O$ 242.44 (for pure material)

Cetyl alcohol, used in pharmaceutical preparations, is a mixture of solid aliphatic alcohols comprising mainly 1-hexadecanol ($C_{16}H_{34}O$). The USP32–NF27 specifies not less than 90.0% of cetyl alcohol, the remainder consisting chiefly of related alcohols. Commercially, many grades of cetyl alcohol are available as mixtures of cetyl alcohol (60–70%) and stearyl alcohol (2030%), the remainder being related alcohols.

Functional Category:

Coating agent; emulsifying agent; stiffening agent.

Solubility:

Freely soluble in ethanol (95%) and ether, solubility increasing with increasing temperature; practically insoluble in water. Miscible when melted with fats, liquid and solid paraffins, and isopropyl myristate.

Applications in pharmaceutical formulation or technology:

Cetyl alcohol is widely used in cosmetics and pharmaceutical formulations such as suppositories, modified-release solid dosage forms, emulsions, lotions, creams, and ointments. In suppositories cetyl alcohol is used to raise the melting point of the base, and in modified-release dosage forms it may be used to form a permeable barrier coating. In lotions, creams, and ointments cetyl alcohol is used because of its emollient, water-absorptive, and emulsifying properties. It enhances stability, improves texture, and increases consistency. The emollient properties are due to absorption and retention of cetyl alcohol in the epidermis, where it lubricates and softens the skin while imparting a characteristic 'velvety' texture.

Cetyl alcohol is also used for its water absorption properties in water-in-oil emulsions. For example, a mixture of petrolatum and cetyl alcohol (19 : 1) will absorb 40–50% of its weight of water.

Cetyl alcohol acts as a weak emulsifier of the water-in-oil type, thus allowing a reduction of the quantity of other emulsifying agents used in a formulation. Cetyl alcohol has also been reported to increase the consistency of water-in-oil emulsions. In oil-in-water emulsions, cetyl alcohol is reported to improve stability by combining with the water-soluble emulsifying agent. The combined mixed emulsifier produces a close packed, monomolecular barrier at the oil–water interface which forms a mechanical barrier against droplet coalescence.

In semisolid emulsions, excess cetyl alcohol combines with the aqueous emulsifier solution to form a viscoelastic continuous phase that imparts semisolid properties to the emulsion and also prevents droplet coalescence. Therefore, cetyl alcohol is sometimes referred to as a 'consistency improver' or a 'bodying agent',

although it may be necessary to mix cetyl alcohol with a hydrophilic emulsifier to impart this property.

It should be noted that pure or pharmacopeial grades of cetyl alcohol may not form stable semisolid emulsions and may not show the same physical properties as grades of cetyl alcohol that contain significant amounts of other similar alcohols.

Stability and Storage conditions:

Cetyl alcohol is stable in the presence of acids, alkalis, light, and air; it does not become rancid. It should be stored in a well-closed container in a cool, dry place.

5.2.3.Stearic acid: *(Raymond C. R., et al., 2009)*

Nonproprietary names:

BP : Stearic Acid

JP : Stearic Acid

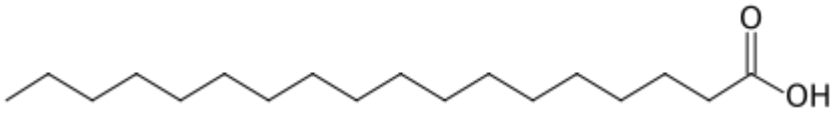
PhEur : Stearic Acid

USP-NF : Stearic Acid

Synonyms:

Acidum stearicum; cetylacetic acid; Crodacid; Cristal G; Cristal S; Dervacid; E570; Edenor; Emersol; Extra AS; Extra P; Extra S; Extra ST; 1-hepta decane carboxylic acid; Hystrene; Industrene; Kortacid 1895; Pearl Steric; Pristerene; stereophanic acid; Tegostearic.

Structural formula:



Chemical name and CAS registry number:

Octadecanoic acid [57-11-4]

Description:

Stearic acid is a hard, white or faintly yellow-colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor (with an odor threshold of 20 ppm) and taste suggesting tallow.

Melting point:

66-69°C

Empirical formula and molecular weight:

$C_{18}H_{36}O_2$ 284.47 (for pure material)

The USP32–NF27 describes stearic acid as a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$). In the USP32– NF27, the content of stearic acid is not less than 40.0% and the sum of the two acids is not less than 90.0%.

The USP32–NF27 also contains a monograph for purified stearic acid; The PhEur 6.5 contains a single monograph for stearic acid but defines stearic acid 50, stearic acid 70, and stearic acid 95 as containing specific amounts of stearic acid ($C_{18}H_{36}O_2$).

Functional Category:

Emulsifying agent; solubilizing agent; tablet and capsule lubricant

Applications in pharmaceutical formulation or technology:

Stearic acid is widely used in oral and topical pharmaceutical formulations. It is mainly used in oral formulations as a tablet and capsule lubricant; although it may also be used as a binder or in combination with shellac as a tablet coating. It has also been suggested that stearic acid may be used in enteric tablet coatings and as a sustained-release drug carrier. In topical formulations, stearic acid is used as an emulsifying and solubilizing agent. When partially neutralized with alkalis or triethanolamine, stearic acid is used in the preparation of creams. The partially neutralized stearic acid forms a creamy base when mixed with 5–15 times its own

weight of aqueous liquid, the appearance and plasticity of the cream being determined by the proportion of alkali used.

Stearic acid is used as the hardening agent in glycerin suppositories. Stearic acid is also widely used in cosmetics and food products.

Stability and storage:

Stearic acid is a stable material; an antioxidant may also be added to it. The bulk material should be stored in a wellclosed container in a cool, dry place.

5.2.4. Lactose: ***(****Raymond C. R., et al., 2009)*

Nonproprietary names:

BP : Lactose

PhEur : Lactose Monohydrate

JP : Lactose Hydrate

USP : Lactose Monohydrate

Synonyms:

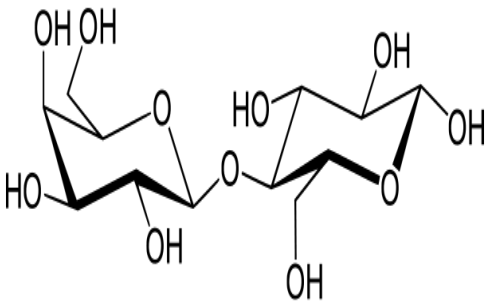
CapsuLac; GranuLac; Lactochem; lactosum monohydricum; Monohydrate; Pharmatose; PrismaLac; SacheLac; SorboLac; SpheroLac; SuperTab 30GR; Tablettose.

Chemical name and CAS registry number:

O-b-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate [5989-81-1]; [10039-26-6]; [64044-51-5] CAS Registry numbers for lactose monohydrate are

[5989-81- 1] (lactose monohydrate), [10039-26-6] (lactose monohydrate, cyclic), and [64044-51-5] (lactose monohydrate, open form).

Structural formula:



Empirical Formula and Molecular Weight:

$C_{12}H_{22}O_{11}\_H_2O$ 360.31

Functional category:

Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluent; tablet and capsule filler.

Description:

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. alactose monohydrate, b-lactose anhydrous, and a-lactose anhydrous.

The stable crystalline forms of lactose are a-lactose monohydrate, b-lactose anhydrous, and stable a-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; a-lactose is approximately 20% as sweet as sucrose, while b-lactose is 40% as sweet.

Moisture content:

Lactose monohydrate contains approximately 5% w/w water of crystallization and normally has a range of 4.5–5.5% w/w water content.

Applications in pharmaceutical formulation or technology:

Lactose is widely used as a filler and diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas.(1–9) Lactose is also used as a diluent in dry-powder inhalation; seeLactose, Inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics. This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used.

364 Lactose, Monohydrate Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size allows better mixing with other formulation ingredients and utilizes the binder more efficiently.

Other applications of lactose include use in lyophilized products, where lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose (approximately 1 : 3) to prepare sugar-coating solutions. It may also be used in intravenous injections.

Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Direct-compression grades of lactose monohydrate are available as granulated/agglomerated a-lactose monohydrate, containing small amounts of anhydrous lactose. Direct-compression grades are often

used to carry lower quantities of drug and this permits tablets to be made without granulation.

Stability and storage conditions:

Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; The purities of different lactoses can vary and color evaluation may be important, particularly if white tablets are being formulated. The color stabilities of various lactoses also differ. Solutions show mutarotation;

Lactose should be stored in a well-closed container in a cool, dry place.

5.2.5. Talc: ***(****Raymond C. R., et al., 2009)*

Nonproprietary names:

BP **:** Purified talc

JP **:** Talc

PhEur **:** Talcum

USPNF **:** Talc

Synonyms:

Purified chalk, altalc, powdered talc and soapstone

Chemical name and CAS registry number:

Talc [14807-96-6]

Description:

A very fine, white to grayish white, impalpable, odorless crystalline powder, Unctuous, adheres readily to skin, soft to touch and free from granules.

Empirical formula:

$Mg_6 (Si_2O_5)_4(OH)_4$

Functional category:

Tablet, capsule it can use as a lubricant and diluents. During compression used as glidant and anticaking agent.

Solubility:

Insoluble in water, organic solvents, dilutes acids and alkalis.

Storage conditions:

Stable, Preserve in a well-closed container in a cool, dry place.

MATERIALS AND EQUIPMENTS

6. MATERIALS AND EQUIPMENTS

6.1. Materials used:

Table 6.1: List of materials with source

S.No.	Name of Ingredients	Name of supplier
1	Venlafaxine Hydrochloride	Orchid pharmaceuticals, Puducherry.
2	Carnauba wax	Shasun pharmaceuticals, Puducherry.
3	Cetyl alcohol	Tristar formulations Pvt. Ltd., Puducherry.
4	Stearic acid	Tristar formulations Pvt. Ltd., Puducherry.
5	Lactose	Loba chemie Pvt.Ltd., Mumbai.
6	Talc	Loba chemie Pvt.Ltd., Mumbai.
7	Hydrochloric acid	S d fine-chem limited, Mumbai.
8	Methanol	Qualigens fine chemicals, Mumbai.
9	Acetone	Loba chemie Pvt.Ltd., Mumbai.
10	Sodium hydroxide	S d fine-chem limited, Mumbai.

6.2. Equipments used:

Table 6.2: List of equipments with model/make

S.No.	Equipment	Model/ Make
1	Electronic balance	Shimadzu BL-220H, Japan.
2	Bulk density apparatus	Indolabs VTAP/MATIC-II, Chennai.
3	Standard sieves	Jayant scientific, India.
4	Hot air oven	Precision scientific Co., Chennai.
5	Sixteen punch tablet compression machine	Cadmach, Ahmadabad, India.
6	Friability apparatus	Veego scientific VFT-DV, Mumbai.
7	Hardness tester	Monsanto
8	Vernier caliper	Indolabs, Mitutoyo.
9	Humidity chamber	Labtech, Ambala.
10	USP dissolution test apparatus Type I	Veego scientific VDA-8DR, Mumbai.
11	UV-Visible spectrophotometer	Elico-SL 159 UV-Visible spectrophotometer, Japan.
12	FTIR spectrophotometer	Shimadzu, Japan.
13	Differential scanning calorimeter	Shimadzu, Japan.

EXPERIMENTAL WORK

7. EXPERIMENTAL WORK

7.1. Preformulation study:

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone. It is the first step in rational development of dosage form.

7.1.1. Identification of drug:

7.1.1.1. Identification by FTIR spectroscopy: *(IP, 2007; Skoog D.A., et al., 2004)*

Venlafaxine Hydrochloride discs were prepared by pressing the Venlafaxine Hydrochloride with potassium bromide and the spectra ranges between 4000 to 400 cm^{-1} was obtained under the operational conditions. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

7.1.1.2. Identification by melting point: *(IP, 2007)*

Melting point of the drug was determined by capillary tube method.

7.1.2. Physicochemical parameters:

7.1.2.1. Organoleptic properties: ***(****Lachman L., et al., 1991; Banker G.S. and Rhodes C.T., 1996)*

The color, odor and taste of the drug were recorded using descriptive terminology.

7.1.2.2. Solubility study: *(IP, 2007)*

It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in Indian Pharmacopoeia, 2007.

7.1.2.3. Loss on drying: *(IP, 2007)*

Loss on drying was the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified condition. The accurately weighed 1gm of sample was transferred in glass-stoppered, shallow weighing bottle and accurately weighed the bottle. The bottle was transferred in oven and substance was dried at 105°C for 3 hours. The bottle was removed from oven and reweighed; loss on drying was calculated by following equation,

$$\mathbf{LOD} = \frac{\mathbf{Initial\ weight\ of\ substance - Final\ weight\ of\ substance}}{\mathbf{Initial\ weight\ of\ substance}} \times \mathbf{100}$$

7.1.3. Analytical methods:

7.1.3.1. . Determination of λ max: *(Patil Prakash., et al., 2011)*

The absorption maximum of the standard solution was scanned between 200-400 nm regions on Shimadzu-1700 Pharmaspec UV-Visible spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

7.1.3.2. Preparation of standard curve of Venlafaxine Hydrochloride in 0.1N HCl: *(Patil Prakash., et al., 2011)*

A stock solution of Venlafaxine Hydrochloride was prepared by dissolving 100 mg of drug in 0.1 N HCl and final volume was made to 100 ml to give a solution concentration 1000 µg/ml. From the stock solution, 10 ml was pipettted out into 100 ml volumetric flask to obtain concentration of 100µg/ml. From the standard stock solution of Venlafaxine Hydrochloride, appropriate aliquots of 1, 2, 3, 4 and 5 ml were pipetted out into 25 ml volumetric flask and final volume was made with 0.1 N HCl. To obtained concentration of 4, 8, 12, 16 and 20 µg/ml. Absorbance spectra of each solution against 0.1 N HCl as blank were measured at 225.5 nm using Elico-SL 159 UV-Visible spectrophotometer.

7.1.3.4. Preparation of standard curve of Venlafaxine Hydrochloride in pH 6.8 phosphate buffer: *(Patil Prakash., et al., 2011)*

A stock solution of Venlafaxine Hydrochloride was prepared by dissolving 100 mg of drug in pH 6.8 and final volume was made to 100 ml to give a solution concentration 1000 µg/ml. From the stock solution, 10 ml was pipettted out into 100 ml volumetric flask to obtain concentration of 100µg/ml. From the standard stock solution of Venlafaxine Hydrochloride appropriate aliquots of 1, 2, 3, 4 and 5 ml were pipetted out into 50 ml volumetric flask and final volume was made with pH 6.8. To obtained concentration of 4, 8, 12, 16 and 20 µg/ml. Absorbance spectra of each solution against pH 6.8 as blank were measured at 226 nm using Elico-SL 159 UV-Visible spectrophotometer.

7.1.3.5. Determination of Percentage purity of Drug: *(Patil Prakash., et al., 2011)*

Accurately weighed 100 mg of Venlafaxine Hydrochloride was dissolved in little quantity of pH 6.8 Phosphate buffer and volume was adjusted to 100 ml with the same to prepared standard solution having concentration of 1000 µg/ml. From the above solution, aliquots of 5 ml were transferred to 25 ml volumetric flasks and final volume was made up to 25 ml with pH 6.8. Absorbance values of these solutions were measured against blank (pH 6.8) at 225.5 nm using UV-VISIBLE spectrophotometer. The percentage purity of drug was calculated by using calibration graph method (least square method).

7.1.4. Determination of drug-polymer compatibility: ***(****Aulton M.E., 2007)*

Differential scanning calorimetry, Fourier transforms infrared spectroscopy studies were used for the evaluation of physicochemical compatibility and interaction, which helps in the prediction of interaction of the drug and polymers. Each polymer used in the formulations was blended with the drug levels that are realistic with respect to the final dosage form. Each polymer was thoroughly blended with drug to increase drug- polymer molecular contacts to accelerate the reactions if possible.

7.1.4.1. Fourier transform infrared spectroscopy: *(Bhalekar., et al., 2008; Jadhav Sunita.,et al., 2011; Silverstein R.M., 2003)*

FTIR studies are very helpful in the evaluation of drug polymer interaction studies. If there is any incompatibility between the drug and polymer, these can be predicted by changes in the functional peaks. Infrared spectrum of Venlafaxine

Hydrochloride was determined on Fourier transform infrared spectrophotometer using potassium bromide dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and various polymers were thoroughly mixed with potassium bromide. The crushed powders were compressed using a hydraulic compactor at approximately 20,000 pounds under vacuum for 3 minutes. FTIR instrument were performed under nitrogen atmosphere at a flow rate of 50 standard cubic feet per hour. Spectral scanning was conducted from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1} by using Shimadzu (Japan) FTIR spectrophotometer.

7.1.4.2. Differential scanning calorimetry: *(Atul A. Bodkhe.,et al., 2010)*

Any possible drug polymer interaction can be studied by thermal analysis. The DSC analysis of pure drug, drug with carnauba wax were carried out using Shimadzu to evaluate any possible drug-polymer interaction. The 2 mg sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºC at heating rate of 10ºC /min under nitrogen flow of 30 ml/min.

7.1.5. Formulation of Venlafaxine Hydrochloride sustained release matrix tablets: *(Bhalekar., et al., 2008)*

All the ingredients mentioned in Table 7.1 were pre-weighed and passed the drug through mesh #80. The waxes were molten and then required quantity of drug was slowly added to the molten wax. After cooling, the mass was subjected to granulation by passing through mesh #16. Granules were mixed with lactose and talc and also used for evaluation of flow characteristic.

Table 7.1: Composition of Venlafaxine Hydrochloride SR matrix tablets

Ingredients	VF1	VF2	VF3	VF4	VF5	VF6	VF7	VF8	VF9
Venlafaxine Hydrochloride	75	75	75	75	75	75	75	75	75
Carnauba wax	53	106	159	-	-	-	-	-	-
Cetyl alcohol	-	-	-	53	106	159	-	-	-
Stearic acid	-	-	-	-	-	-	53	106	159
Lactose	204	151	98	204	151	98	204	151	98
Talc	18	18	18	18	18	18	18	18	18
Total weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

All the quantities are expressed as mg per tablet.

7.1.6. Evaluation of pre-compression granules:

7.1.6.1. Angle of repose: *(Lachman L., et al., 1991)*

The angle of repose was determined by the funnel method. An accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated using the following equation.

$$\tan(\theta) = \frac{h}{r}$$

Where '**h**' and '**r**' are the height and radius respectively of the powder cone.

Table 7.2: Standard values of angle of repose (°)

S. No.	Flowability	Angle of repose
1	Excellent	<25
2	Good	25-30
3	Passable*	30-40
4	Poor	37-45
5	Very poor	>45

* Adding glidant for improving flow

7.1.6.2. Loose bulk density: *(Lachman L., et al., 1991)*

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The loose bulk density of powder blends was determined using the following formula.

Loose bulk density = Total weight of powder / Total volume of powder

7.1.6.3. Tapped bulk density: *(Lachman L., et al., 1991)*

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped bulk densities of powder blends were determined using the following formula.

Tapped bulk density= Total weight of powder / Total volume of tapped powder

7.1.6.4. Hausner's ratio: *(Aulton M.E., 2007)*

It is related to interparticulate friction and could be used to predict powder flow properties. Hausner's ratio was determined by following equation,

Hausner's Ratio = Tapped bulk density / Loose bulk density

A Hausner ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.

7.1.6.5. Carr's compressibility index: *(Aulton M.E., 2007)*

It is a simple index that can be determined on small quantities of powder. The compressibility indices of the powder blends was determined using following formula,

Carr's compressibility index (%) = [(TBD-LBD)/ TBD] x100

Relationship between % compressibility and flowability is shown in the table 7.3.

Table 7.3: Standard values of Carr's index

S. No.	Carr's index	Type of flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-35	Poor*
5	33-38	Very poor*
6	>40	Extremely poor*

* May be improved by glidant

7.2. Preparation of SR Matrix Tablets: *(Atul A. Bodkhe., et al., 2010)*

Hot melt granulation method:

All the ingredients metioned in Table 7.1 were pre-weighed and passed the drug through mesh #80. The waxes were molten and then required quantity of drug was slowly added to the molten wax. After cooling, the mass was subjected to granulation by passing through mesh #16. Granules were mixed with lactose and talc and compressed on a 16- station rotary tablet compression machine using 11mm round, biconcave punches.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 350 mg with different drug polymer ratios like 1:0.7, 1:1.4, and 1:2.1. The various polymers used were carnauba wax, cetyl alcohol and stearic acid.

In the formulations prepared, the release retardants included were carnauba wax, cetyl alcohol and stearic acid. Lactose is used as diluent and talc 5 % were used as lubricant and glidant.

7.3. Evaluation of Venlafaxine Hydrochloride sustained release matrix tablets:

7.3.1. Appearance: ***(****Lachman L., et al., 1991)*

The tablets were visually observed for capping, chipping and lamination.

7.3.2. Dimension (Thickness and Diameter): ***(****Lachman L., et al., 1991)*

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined by using Vernier

caliper. Ten tablets from each type of formulation were used and average values were calculated.

7.3.3. Tablet hardness: ***(****Lachman L., et al., 1991)*

For each formulation, the hardness of 10 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2.

7.3.4. Percent friability: ***(****Lachman L., et al., 1991)*

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows.

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

7.3.5. Weight variation: ***(****IP, 2007; Lachman L., et al., 1991)*

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and

individual tablet weight was then compared with average value to find the deviation in weight. The test was performed according to the official method.

Weight variation importance during tablets compression section, each and every time intervals we must check the weight of tablet. If we are not maintaining the weight variation means it will give the deviation of drug content as well as yield of tablets.

Table 7.4: Specifications of % weight variation allowed in tablets as per Indian Pharmacopoeia

S. No.	Average weight of tablets (mg)	Maximum percent deviation allowed (%)
1	80 or less	10
2	More than 80 but less than 250	7.5
3	More than 250	5

7.3.6. Drug content: *(Patil Prakash., et al., 2011)*

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to 100 mg of Venlafaxine Hydrochloride was transferred into a 100 ml standard volumetric flask. Then added 50ml of pH 6.8 phosphate buffer solution. It was gently shaken for 15 minutes. Then made upto the mark with pH 6.8 phosphate buffer solution. The solution was filtered through a whatmann filter paper, diluted suitably and the absorbance of resultant solution was measured by using Elico-SL 159 UV-Visible spectrophotometer at 226nm using pH 6.8 phosphate buffer as blank.

7.3.7. *In vitro* release studies: *(Atul A. Bodkhe., et al., 2010)*

The release rate of Venlafaxine Hydrochloride from matrix tablets was determined using United States Pharmacopoeia dissolution testing apparatus I (Basket method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed at 50 rpm using 900 ml of pH 1.2 for the first 2 hrs and phosphate buffer pH 6.8 from 2-10 hrs at 37 ± 0.5°C. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted suitably. Absorbance of these solutions was measured at 226 nm using Elico-SL 159 UV-Visible spectrophotometer. For each formulation, the experiments were carried out in triplicate. The release data were analyzed to study the release kinetics using zero order, first order and matrix, korsmeyer-peppas equations by using PCP disso V3 software.

7.3.8. Kinetics of *in vitro* drug release: *(Brahmankar D.M. and Jaiswal S.B., 2009; Mukesh C. Gohel., et al., 2012)*

To study the release kinetics of *in vitro* drug release, the data was applied to kinetic models such as zero order, first order, higuchi and korsmeyer- Peppas.

- **Zero order**

$$C = K_0 t$$

Where K_0 - Zero-order rate constant expressed in units of concentration/time

t - Time in hrs.

- **First order**

$$\mathbf{LogC = LogC_0 - Kt / 2.303}$$

Where C_0 - Initial concentration of drug,

K - First order constant and t - Time in hrs.

- **Higuchi**

$$\mathbf{Q_t = Kt^{1/2}}$$

Where Q_t - Amount of the release drug in time t,

K- Kinetic constant and t- is time in hrs

- **Korsmeyer Peppas**

$$\mathbf{M_t / M_\infty = Kt\ n}$$

Where, Mt - represents amount of the released drug at time t,

M_∞- Overall amount of the drug (whole dose) released after 12 hrs

K- Diffusion characteristic of drug/ polymer system constant

n- Diffusion exponent that characterizes the mechanism of release of drug.

Table 7.5: Diffusion exponent and solute release mechanism

Diffusion exponent (n)	**Overall solute diffusion mechanism**
0.45	Fickian diffusion
0.45<n <0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n>0.89	Super case-II transport

7.4. Stability study: *(Atul A. Bodkhe., et al., 2010)*

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted.

ICH specifies the length of study and storage conditions

- **Long-Term Testing**: 25°C ± 2°C at 60% RH ± 5% for 12 Months
- **Accelerated Testing:** 40°C ± 2°C at 75% RH ± 5% for 6 Months

In present study the selected formulation VF3 exposure up to 3 months stability studies at accelerated condition (40°C ± 2°C at 75% RH ± 5% RH) to find out the effect of aging on hardness, friability, drug content and *in vitro* drug release.

Stability studies were carried out at accelerated condition (40°C ± 2°C at 75% RH ± 5% RH) for the optimized formulation VF3. The matrix tablets were stored at 40°C ± 2°C at 75% RH ± 5% RH for accelerated temperature in closely packed with aluminium foil for 3 months. The samples were withdrawn after periods of 1st month, 2nd month and 3rd month. The samples were analyzed for its hardness, drug content and *in vitro* drug release.

RESULTS AND DISCUSSION

8. RESULTS AND DISCUSSION

8.1. Preformulation parameters:

8.1.1. Identification of drug:

8.1.1.1. Identification by FTIR spectroscopy:

The FTIR spectrum of Venlafaxine Hydrochloride was shown in Figure 8.1 and the interpretations of FTIR frequencies were showed in Table 8.1.

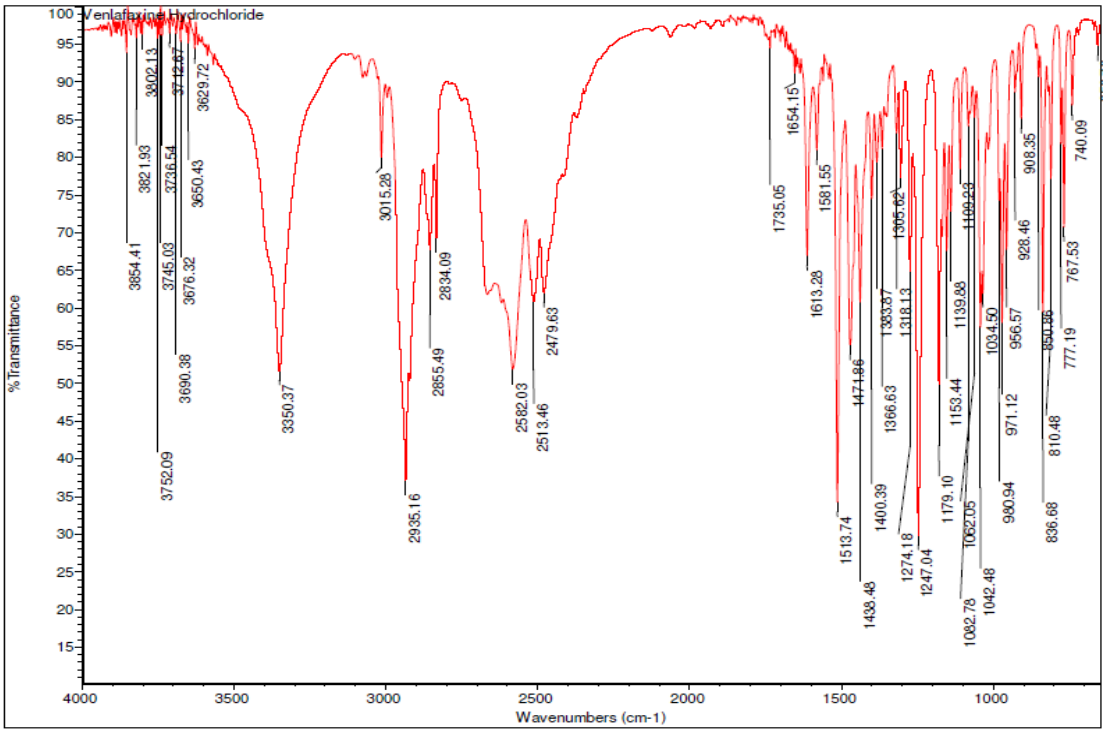


Figure 8.1: FTIR spectrum of Venlafaxine Hydrochloride

- **Interpretation of FTIR Spectrum:**

Major functional groups present in Venlafaxine Hydrochloride shows characteristic peaks in FTIR spectrum. Table 8.1 shows peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks

are identical to functional group of Venlafaxine Hydrochloride. Hence, the sample was confirmed as Venlafaxine Hydrochloride.

Table 8.1: Characteristic frequencies in

FTIR spectrum of **Venlafaxine *Hydrochloride***

Wave No.(cm^{-1})	**Inference**
3015.28	C-H stretching
2935.16	R-O-CH_3 stretching
1318.13	NH_2 stretching
1153.44	OH stretching
1042.48	CH_2 stretching
836.68	C-H bending
740.09	OH bending

8.1.1.2. Melting point:

Melting point of Venlafaxine Hydrochloride sample was found to be 216^0C. The reported melting point for Venlafaxine Hydrochloride was in range of 215 to 217^0C. Hence, experimental values are in good agreement with official values.

8.1.2. Physicochemical parameters of drug:

8.1.2.1. Organoleptic properties:

Colour: White or almost white powder

Odour: Odourless

8.1.2.2. Solubility study:

Table 8.2: Solubility of Venlafaxine Hydrochloride in different solvents

Name of solvents	Solubility
Distilled water	Freely Soluble
Methanol	Freely Soluble
Acetone	Sparingly Soluble
Phosphate buffer (pH 6.8)	Soluble
0.1N HCl	Soluble

8.1.2.3. Loss on drying

The percentage loss on drying after 3 hours was represented in Table 8.3.

Table 8.3: Percentage loss on drying for Venlafaxine Hydrochloride

S. No.	Percentage LOD	Average percentage LOD
1	0.107	0.107
2	0.112	
3	0.104	

The sample passes test for loss on drying as per the limit specified (N.M.T.1%).

8.1.3. Analytical methods:

8.1.3.1. Determination of absorption maximum in 0.1 N HCl:

The absorption maximum for Venlafaxine Hydrochloride in 0.1N HCL was found to be 225.5 nm and absorption maximum was shown in Figure 8.2.

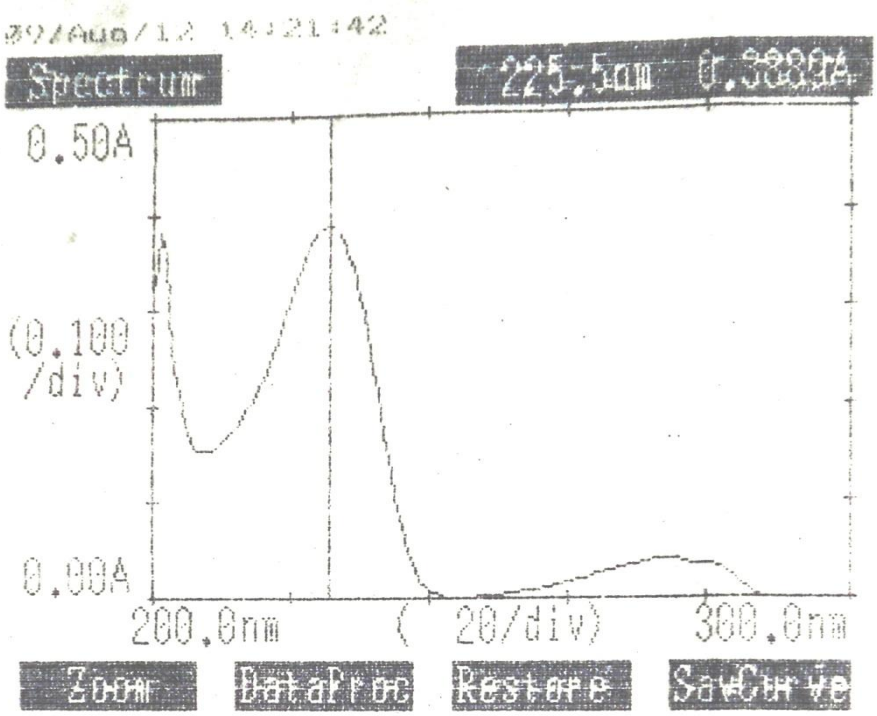


Figure 8.2: λ_{max} observed for Venlafaxine Hydrochloride in 0.1N HCl

8.1.3.2. Determination of absorption maximum in pH 6.8 phosphate buffer:

The absorption maximum for Venlafaxine Hydrochloride in pH6.8 phosphate buffer was found to be 226nm and absorption maximum was shown in Figure 8.3

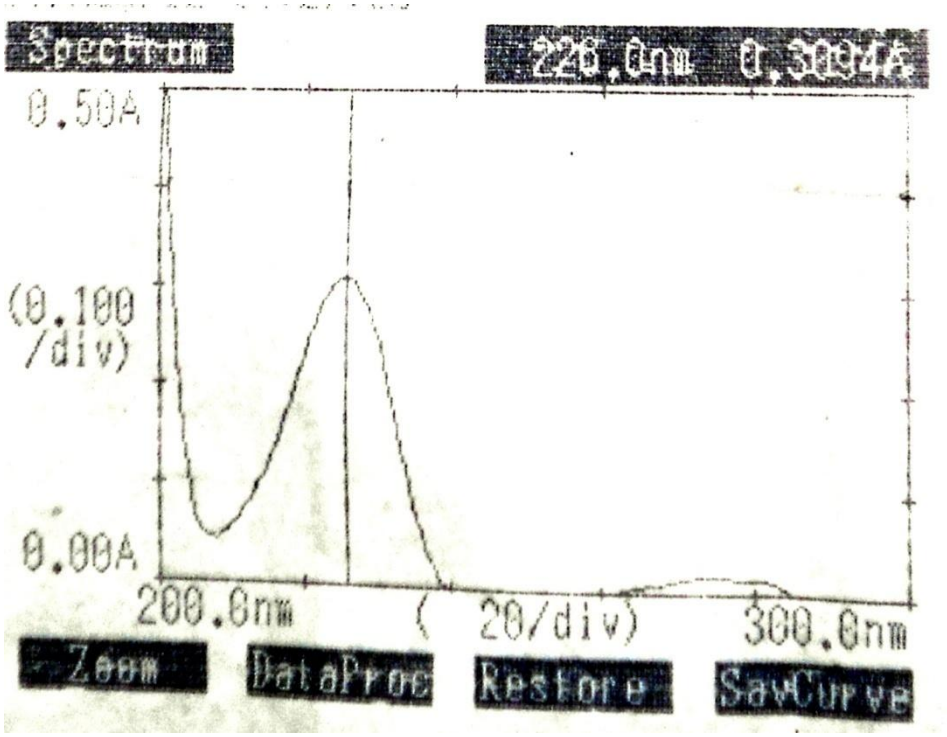


Figure 8.3: λ_{max} observed for Venlafaxine Hydrochloride in pH 6.8 phosphate buffer.

8.1.3.3. Preparation of standard graph of Venlafaxine Hydrochloride in 0.1N HCl:

Absorbance was obtained in various concentrations of Venlafaxine Hydrochloride in 0.1N HCl were given in Table 8.4 and shown in Figure 8.3. The graph of absorbance vs. concentration for Venlafaxine Hydrochloride was found to be linear in the concentration range of 4-20 µg /ml. The calibration curve parameters shown in Table 8.5. So the drug obeys Beer- Lambert's law in the range of 4-20 µg/ml.

Table 8.4: Concentration and absorbance of Venlafaxine Hydrochloride in 0.1N HCl

S. No	Concentration (µg/ml)	Absorbance
1	0	0.000
2	4	0.137
3	8	0.265
4	12	0.390
5	16	0.512
6	20	0.633

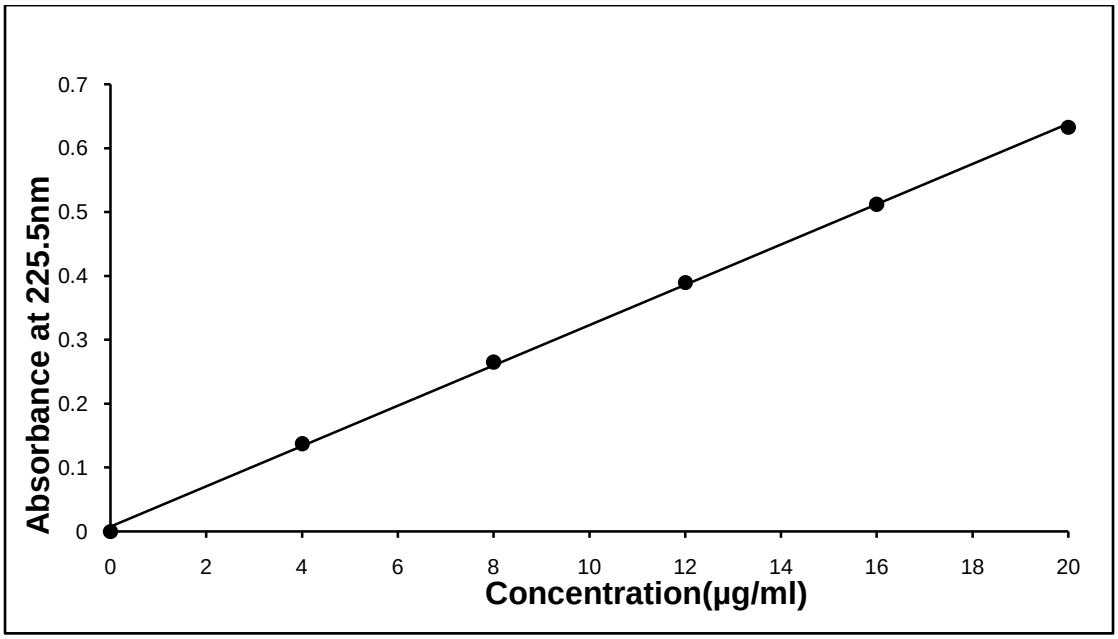


Figure 8.4: Calibration curve of Venlafaxine Hydrochloride in 0.1N HCl

Table 8.5: Calibration parameter values in 0.1 N HCl

S. No	Parameters	Values
1	Correlation coefficient (r)	0.9997
2	Slope (m)	0.0315
3	Intercept (c)	0.0074

8.1.3.4. Preparation of standard graph of Venlafaxine Hydrochloride in pH 6.8 phosphate buffer:

Absorbance obtained for various concentrations of Venlafaxine Hydrochloride in pH 6.8 phosphate buffer were given in Table 8.6 and shown in Figure 8.5. The graph of absorbance vs concentration for Venlafaxine Hydrochloride was found to be linear in the concentration range of 4–20 µg /ml. The calibration curve parameters shown in Table 8.7.So the drug obeys Beer- Lambert's law in the range of 4–20 µg /ml.

Table 8.6: Concentration and absorbance of Venlafaxine Hydrochloride in pH 6.8 phosphate buffer

S. No	Concentration (µg/ml)	Absorbance
1	0	0.000
2	4	0.111
3	8	0.213
4	12	0.312
5	16	0.415
6	20	0.522

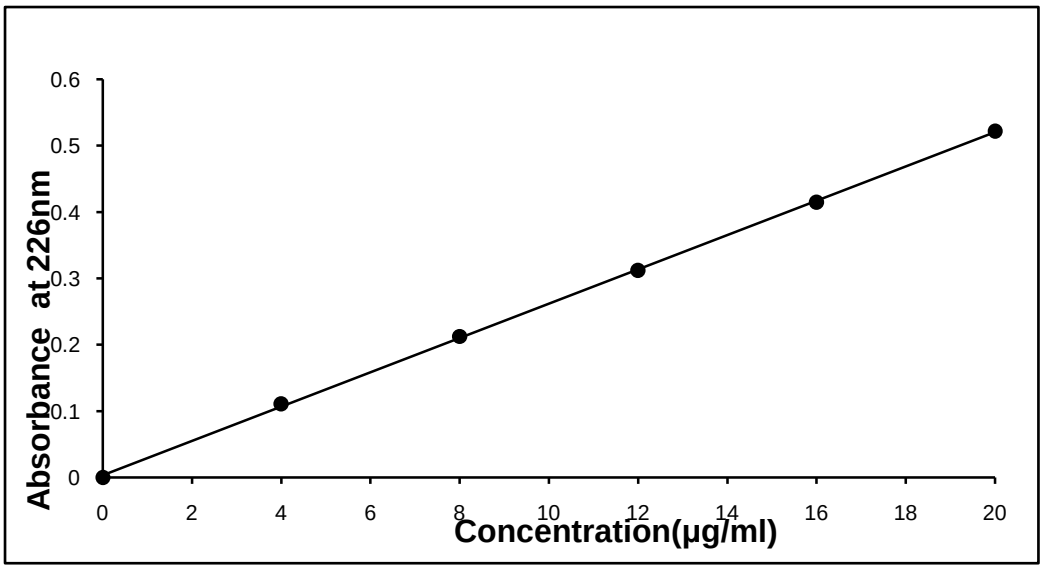


Figure 8.5: Calibration curve of Venlafaxine Hydrochloride in pH 6.8

Table 8.7: Calibration parameter values in pH 6.8 phosphate buffer

S. No	Parameters	Values
1	Correlation coefficient (r)	0.9998
2	Slope (m)	0.0258
3	Intercept (c)	0.0035

8.1.4.3. Percentage purity of drug

The percentage purity of drug was calculated by using calibration graph method and represented in Table 8.8

Table 8.8: Percentage purity of Venlafaxine Hydrochloride in pure drug

S. No.	Percentage purity (%)	Avg. percentage purity (%)
1	99.98	100.09
2	100.12	
3	100.17	

The reported percentage purity for Venlafaxine Hydrochloride was 99 to 102% .

8.1.4. Compatibility testing of drug with polymer:

Compatibility of drug and polymers was found to be as following methods such as Fourier transform infrared spectroscopy and differential scanning calorimetry.

8.1.4.1. Fourier transform infrared spectroscopy:

The FTIR spectrums of Venlafaxine Hydrochloride with different polymers used in formulation are shown in Figures 8.6, 8.7, 8.8 and Table 8.8.

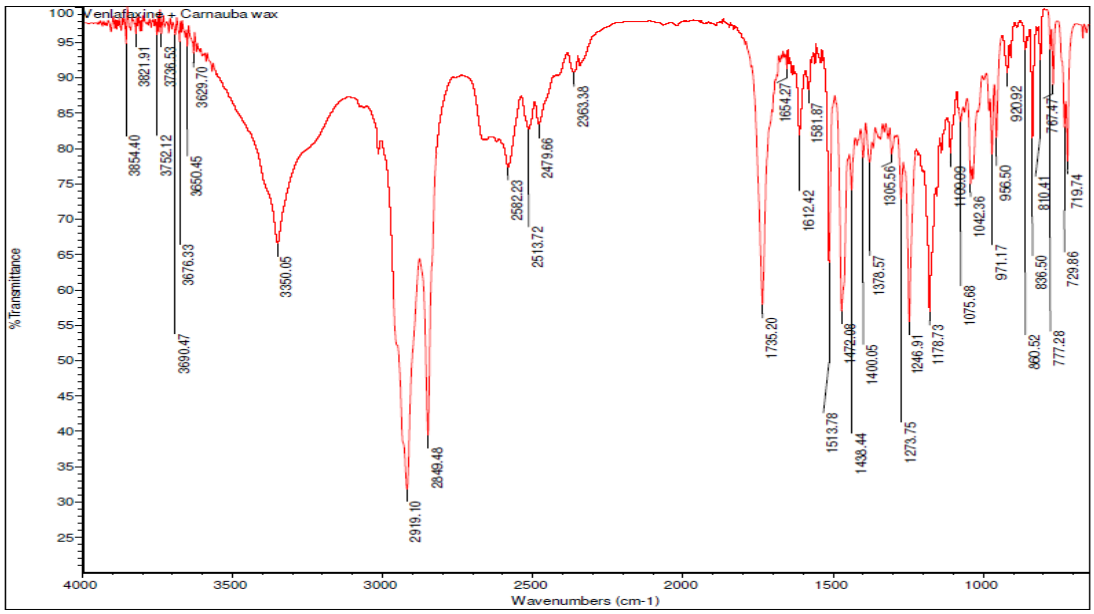


Figure 8.6: FTIR spectrum of Venlafaxine Hydrochloride with carnauba wax

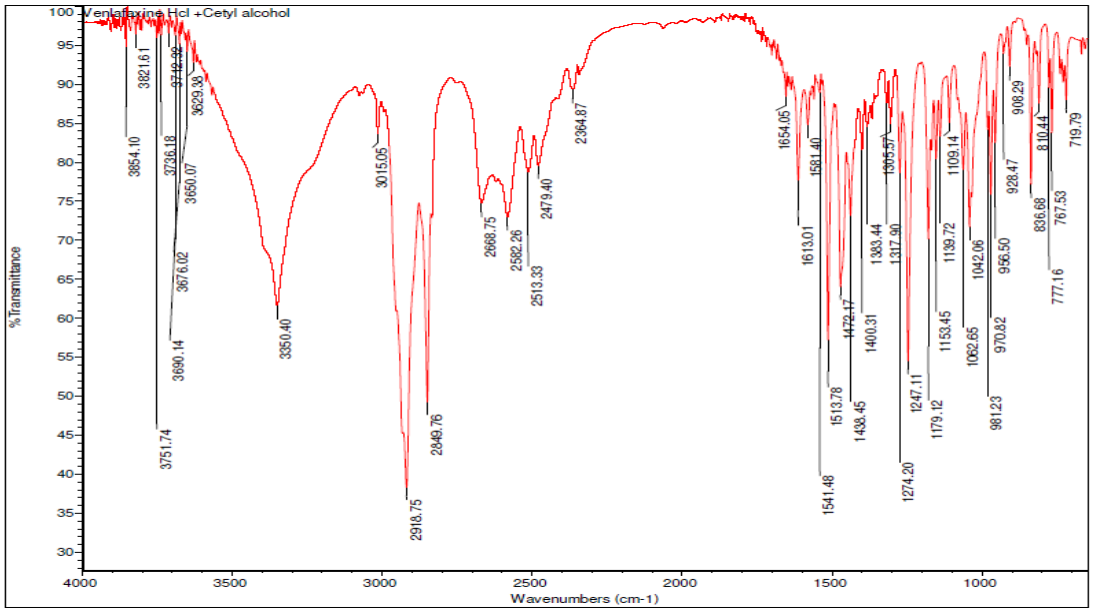


Figure 8.7: FTIR spectrum of Venlafaxine Hydrochloride with cetyl alcohol

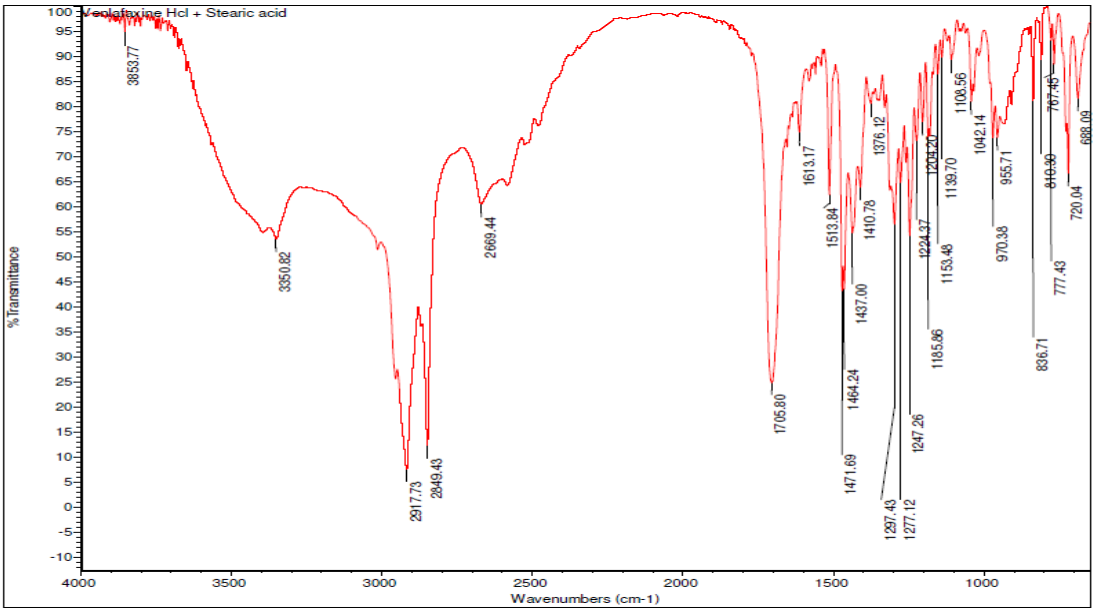


Figure 8.8: FTIR spectrum of Venlafaxine Hydrochloride with stearic acid

Table 8.9: FTIR peaks observed for Venlafaxine Hydrochloride with different polymers used in formulations.

Functional groups	Peaks observed (wave no. (cm^{-1}))			
	Venlafaxine hydrochloride	Venlafaxine hydrochloride + Carnauba wax	Venlafaxine hydrochloride + Cetyl alcohol	Venlafaxine hydrochloride + Stearic acid
C-H stretching	3015.28	3015.19	3015.05	3015.16
R-O-CH_3 stretching	2935.16	2919.10	2918.75	2917.73
NH_2 stretching	1318.13	1305.56	1317.90	1376.12
OH stretching	1153.44	1178.73	1153.45	1153.48
CH_2 stretching	1042.48	1042.36	1042.06	1042.14
C-H bending	836.68	836.50	836.68	836.71
OH bending	740.09	767.47	767.53	767.45

FTIR spectrums were compared, it could indicate that there was no incompatibility between drug and polymer.

According to Table 8.1 and 8.8 and Figures 8.1, 8.6, 8.7 and 8.8, FTIR spectrum showed that there was no major difference in peak when compared between pure drug of Venlafaxine Hydrochloride and Venlafaxine Hydrochloride with different polymers. Therefore it could indicate that there was no incompatibility between drug and different polymers.

8.1.4.2. Differential scanning calorimetry:

The compatibility and interactions between drug and best formulation polymer were checked using differential scanning calorimetry and the results were shown in Figures 8.9 and 8.10

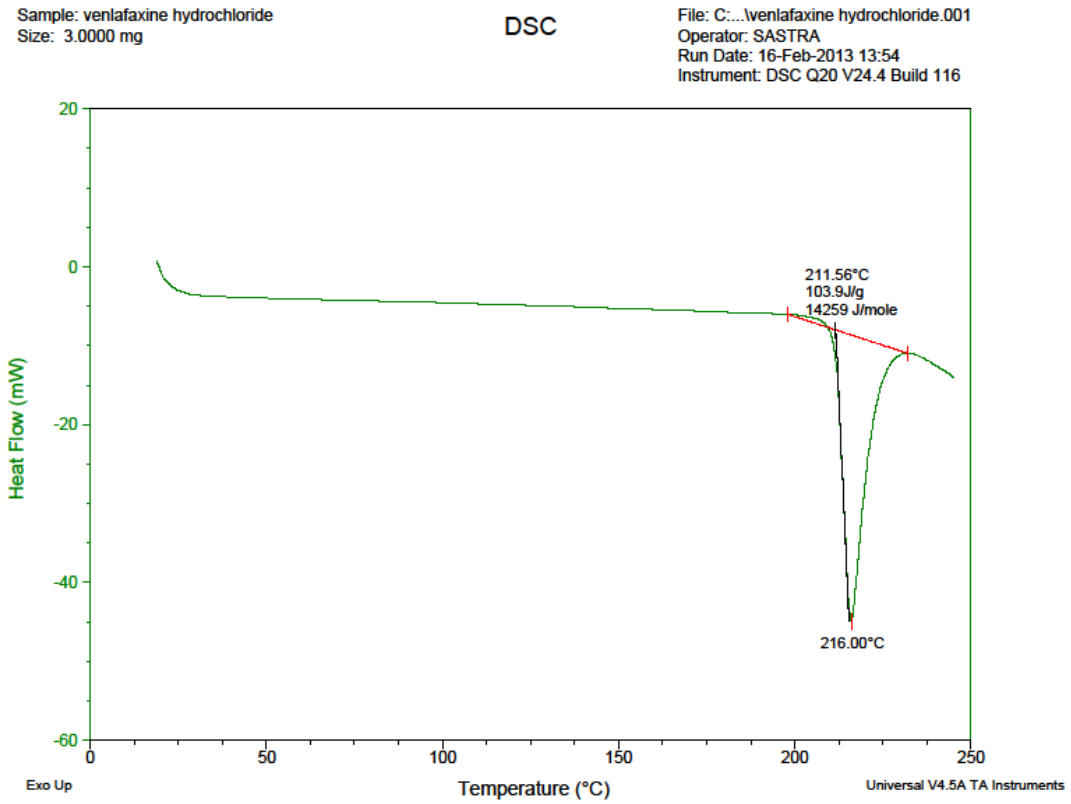


Figure 8.9: DSC thermal analysis of Venlafaxine Hydrochloride

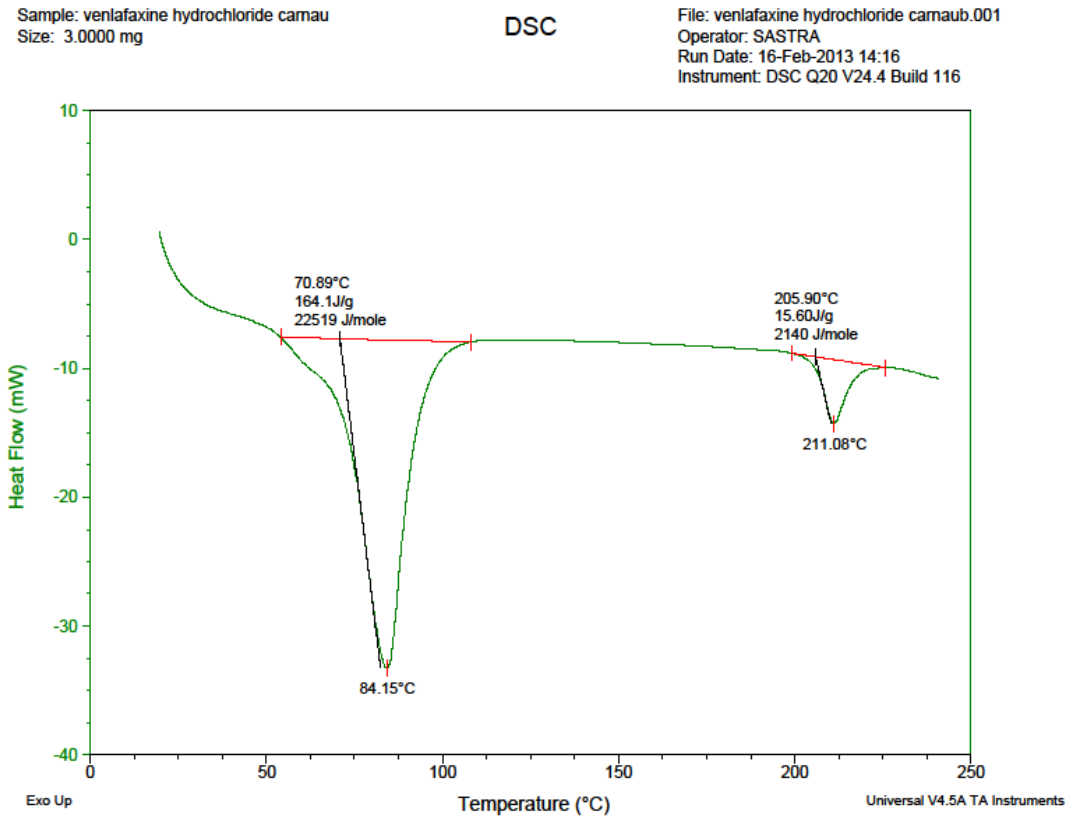


Figure 8.10: DSC thermal analysis of Venlafaxine Hydrochloride + carnauba wax

According to Figures 8.9 and 8.10 and Table 8.10, DSC thermogram showed that there was no major difference in onset temperature and peak temperature when compared with pure drug thermogram. Therefore it could indicate that there was no incompatibility between drug and best formulation polymer.

Table 8.10: DSC thermogram parameters of Venlafaxine Hydrochloride with Carnauba wax

S. No.	DSC thermogram	Onset temperature (°C)	Peak temperature (°C)
1	Venlafaxine Hydrochloride	211.56	216.00
2	Venlafaxine Hydrochloride + carnauba wax	205.90	211.08

According to Figures 8.9 and 8.10 and Table 8.10, DSC thermogram showed that there was no major difference in onset temperature and peak temperature when compared with pure drug's thermogram. No interaction was found between drug and polymer.

8.2. Evaluation of granules:

The granules of different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio. The results of these evaluations were as follows: -

8.2.1. Angle of repose:

Angle of repose ranged from 21.31° ± 0.05 to 23.27° ± 0.43. The results were found to be below 25° and hence the blend was found to have excellent flowability. (Table No. 8.10).

8.2.2. Loose bulk density and tapped bulk density:

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.454 ± 0.00 to 0.476± 0.00 g/ml; and 0.526 ± 0.00 to 0.555 ± 0.00 g/ml respectively. (Table No. 8.10).

Table 8.11: Flow characteristics of powder blends

Formulation Code	Angle of repose (^{o})*	Loose bulk density (g/ml)*	Tapped bulk density (g/ml)*	Hausner ratio*	Carr's index (%)*
VF1	22.43±0.02	0.476±0.00	0.555±0.00	1.16±0.01	14.28±0.62
VF2	21.72±0.01	0.454±0.00	0.526±0.00	1.15±0.00	13.68±0.44
VF3	23.12±0.03	0.476±0.00	0.555±0.00	1.16±0.01	14.28±0.62
VF4	22.23±0.06	0.454±0.00	0.526±0.00	1.15±0.00	13.68±0.44
VF5	21.31±0.05	0.476±0.00	0.555±0.00	1.16±0.00	14.28±0.62
VF6	22.82±0.12	0.476±0.00	0.555±0.00	1.16±0.00	14.28±0.62
VF7	23.27±0.43	0.454±0.00	0.526±0.00	1.15±0.00	13.68±0.44
VF8	22.74±0.39	0.476±0.00	0.555±0.00	1.16±0.00	14.28±0.62
VF9	23.24±0.51	0.454±0.00	0.526±0.00	1.15±0.01	13.68±0.44

*All the values were expressed as mean± SD, n=3

8.2.3. Compressibility index (Carr's index):

The compressibility index (%) ranged from 13.68 ± 0.44 to 14.28 ± 0.62(Table No.8.10). The blend was found to have excellent flowing property as the result were found to be below 15%.

8.2.4. Hausner ratio:

The Hausner ratio ranged from 1.15 ± 0.00 to 1.16± 0.01, (Table No.8.10). The result indicates the free flowing properties of the powders.

8.3. Evaluation of sustained release matrix tablets:

8.3.1. Appearance:

Surface nature of tablets was observed visually and it was concluded they did not show any defects such as capping, chipping and lamination.

8.3.2. Physico-chemical characteristics:

The physical characteristics of Venlafaxine Hydrochloride matrix tablets (VF1 to VF9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and the results were shown in table 8.11.

8.3.2.1. Dimension (Thickness and Diameter):

The size (diameter) of the tablets was found to be in the range from 11.15±0.02 to 11.19± 0.02 mm and thickness ranged between 4.44 ± 0.01 to 4.53 ± 0.01 mm.

8.3.2.2. Tablet hardness:

The hardness of tablets was found to be in the range from 6.05± 0.05 kg/cm^2 to 7.10 ± 0.02 kg/cm^2. This indicates good mechanical strength of tablet.

8.3.2.3. Percent friability:

Percentage friability of all the formulations was found to be in the range from 0.085 to 0.200 %. This indicates good handling property of the prepared matrix tablet.

Table 8.12: Physico-chemical parameters of Venlafaxine Hydrochloride matrix tablets

F. Code	Dimension		Hardness (kg/cm^2)*	Friability (%)*	Weight variation (mg)*	Drug content (%w/w)*
	Diameter (mm)*	Thickness (mm)*				
VF1	11.16±0.01	4.51±0.01	6.70±0.05	0.114±0.03	350.70±0.75	99.43±0.20
VF2	11.19±0.01	4.45±0.02	6.15±0.01	0.185±0.01	353.15±1.12	99.39±0.27
VF3	11.15±0.02	4.53±0.01	7.10±0.02	0.085±0.05	350.81±1.23	99.75±0.11
VF4	11.17±0.02	4.49±0.01	6.50±0.03	0.142±0.07	351.71±1.24	99.31±0.18
VF5	11.16±0.01	4.52±0.01	6.85±0.04	0.100±0.03	350.30±1.68	100.01±0.20
VF6	11.19±0.02	4.44±0.01	6.05±0.05	0.200±0.02	352.86±0.17	99.24±0.41
VF7	11.18±0.02	4.47±0.02	6.30±0.02	0.171±0.01	352.13±1.50	100.03±0.21
VF8	11.17±0.01	4.50±0.01	6.65±0.01	0.128±0.09	351.21±0.10	100.38±0.26
VF9	11.18±0.01	4.48±0.02	6.45±0.03	0.157±0.05	352.10±0.65	99.49±0.24

*All the values were expressed as mean ± SD, n=3.

8.3.2.4. Weight variation:

A tablet is designed to contain a specific amount of drug. When the average weight of the tablet is 400 mg, the pharmacopoeial limit for percentage deviation is ± 5%. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the pharmacopoeial specifications IP 2007.

8.3.2.5. Drug content:

The drug content of all the formulation was found to be in the range from 99.24± 0.41 to 100.38 ± 0.26 % w/w, which was within the specified limit as per IP 2007.

8.3.3. *In vitro* dissolution studies:

Table 8.13: Dissolution profile of formulation VF1

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	16.02±0.93	12.02	8.01	0.50
2	28.63±0.47	21.48	15.17	0.94
3	39.77±0.72	29.83	21.51	1.38
4	50.34±0.94	37.76	27.40	1.82
5	60.21±0.98	45.16	32.98	2.26
6	72.29±0.95	54.22	38.52	2.80
7	80.41±0.73	60.31	43.93	3.18
8	84.41±0.74	63.31	48.74	3.38
9	86.26±0.73	64.70	52.80	3.49
10	88.27±1.00	66.21	56.25	3.63

*****All values were expressed as mean ±SD, n=3.

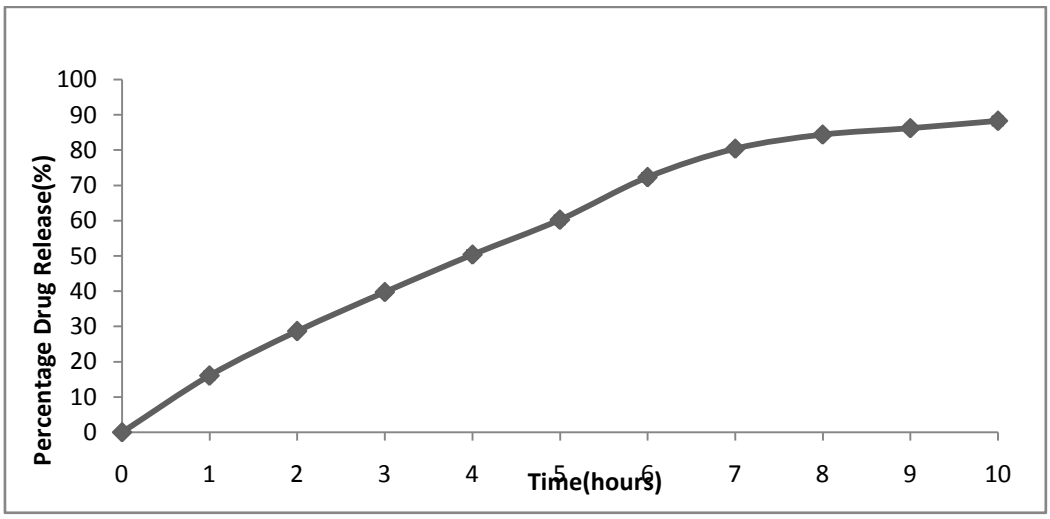


Figure 8.11: *In vitro* drug release profile of formulation VF1

Table 8.14: Dissolution profile of formulation VF2

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	14.78±0.71	11.09	7.39	0.50
2	27.69±0.47	20.77	14.32	0.97
3	35.73±0.92	26.80	20.12	1.31
4	43.35±0.47	32.52	24.97	1.70
5	51.94±0.92	38.96	29.51	2.16
6	62.27±0.71	46.71	34.11	2.71
7	76.99±0.71	57.75	39.19	3.44
8	84.99±0.46	63.75	44.41	3.82
9	87.31±0.93	65.49	49.05	3.94
10	90.89±0.70	68.16	53.05	4.16

*****All values were expressed as mean ±SD, n=3.

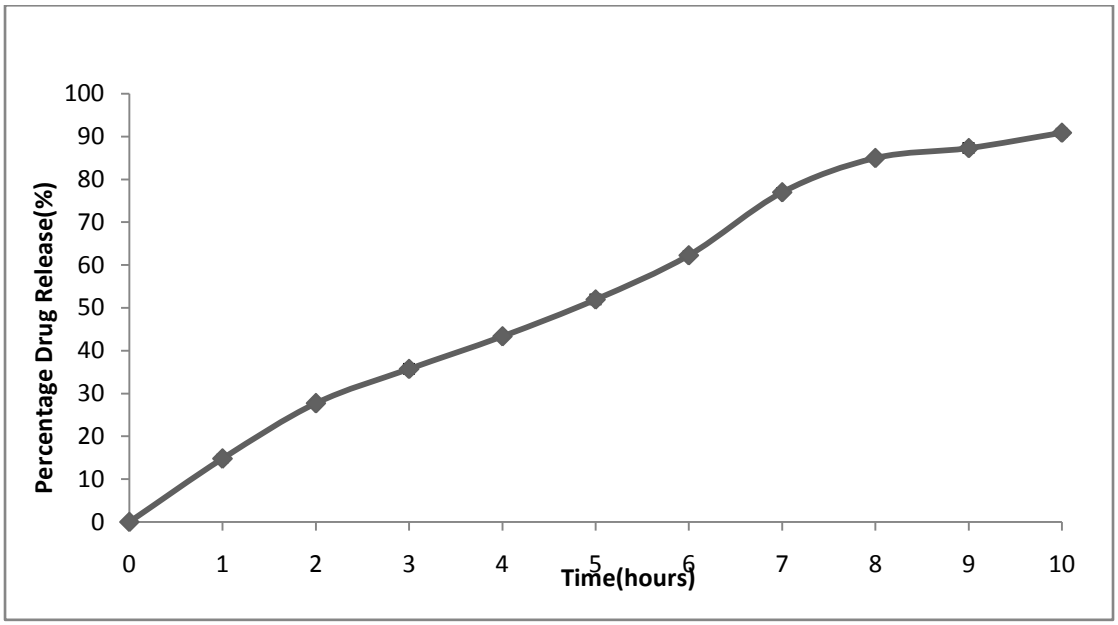


Figure 8.12: *In vitro* drug release profile of formulation VF2

Table 8.15: Dissolution profile of formulation VF3

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	12.31±0.93	9.23	6.15	0.50
2	23.04±0.46	17.29	11.92	0.97
3	30.13±0.93	22.60	16.81	1.33
4	41.43±0.46	31.07	21.55	1.92
5	47.68±0.93	35.77	26.15	2.26
6	56.76±0.45	42.57	30.50	2.78
7	63.10±0.94	47.33	34.70	3.15
8	72.72±0.45	54.54	38.85	3.73
9	81.47±0.94	61.10	43.10	4.24
10	93.04±0.45	69.78	47.52	4.89

*****All values were expressed as mean ±SD, n=3.

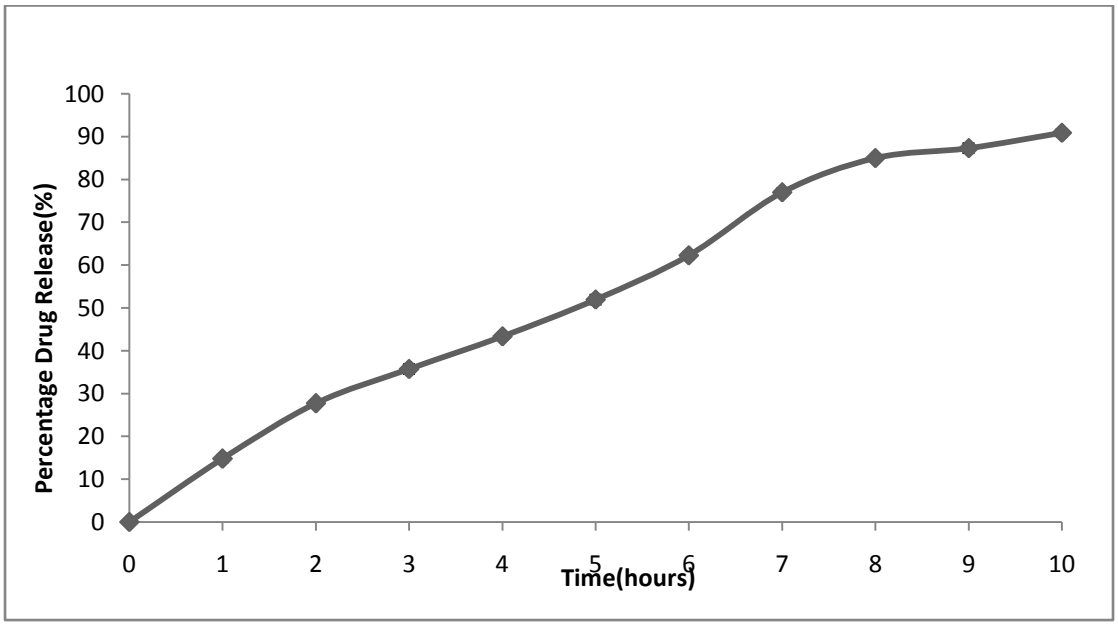


Figure 8.13: *In vitro* drug release profile of formulation VF3

Table 8.16: Dissolution profile of formulation VF4

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	17.87±0.93	13.41	8.94	0.50
2	31.42±0.92	23.57	16.79	0.93
3	49.69±0.46	37.27	24.72	1.51
4	57.85±0.46	43.39	31.98	1.79
5	71.62±0.93	53.72	38.53	2.31
6	74.79±0.46	56.10	44.31	2.45
7	78.45±0.93	58.84	48.93	2.63
8	81.66±0.46	61.25	52.82	2.83
9	82.56±0.93	61.93	56.07	2.89
10	83.47±0.45	62.61	58.77	2.96

*****All values were expressed as mean ±SD, n=3.

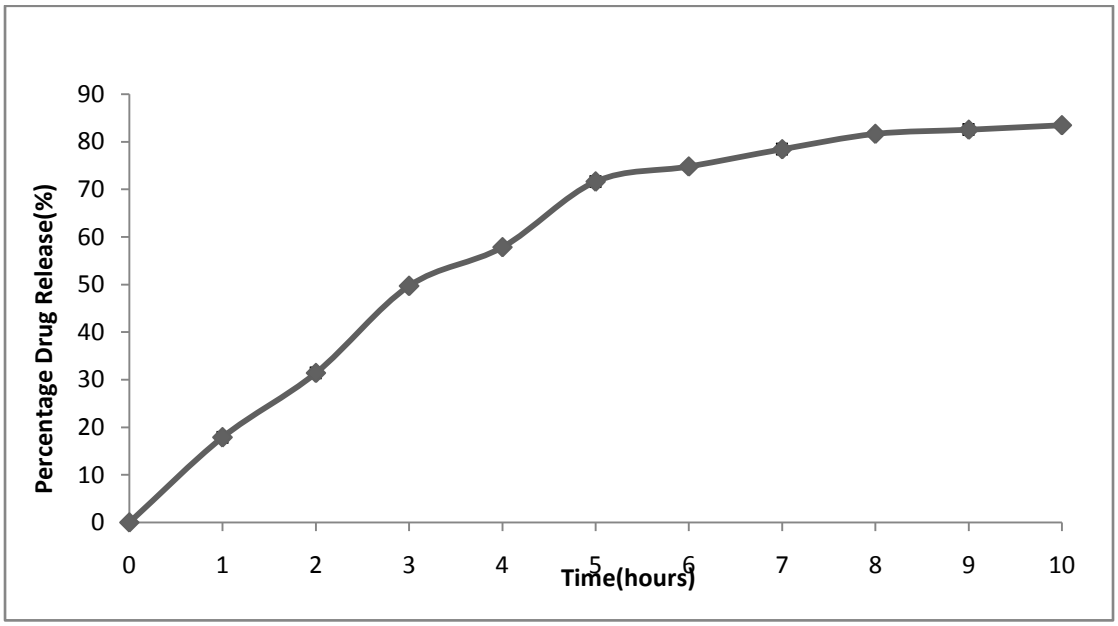


Figure 8.14: *In vitro* drug release profile of formulation VF4

Table 8.17: Dissolution profile of formulation VF5

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	15.09±0.46	11.32	7.55	0.50
2	29.24±0.71	21.94	14.86	0.98
3	38.53±0.93	28.90	21.20	1.35
4	50.03±0.70	37.52	26.97	1.84
5	57.57±0.93	43.18	32.34	2.19
6	60.98±0.71	45.74	36.83	2.38
7	72.13±0.45	54.10	41.07	3.01
8	77.32±1.16	57.99	45.28	3.32
9	82.38±0.71	61.79	49.12	3.63
10	86.07±1.88	64.56	52.63	3.89

*****All values were expressed as mean ±SD, n=3.

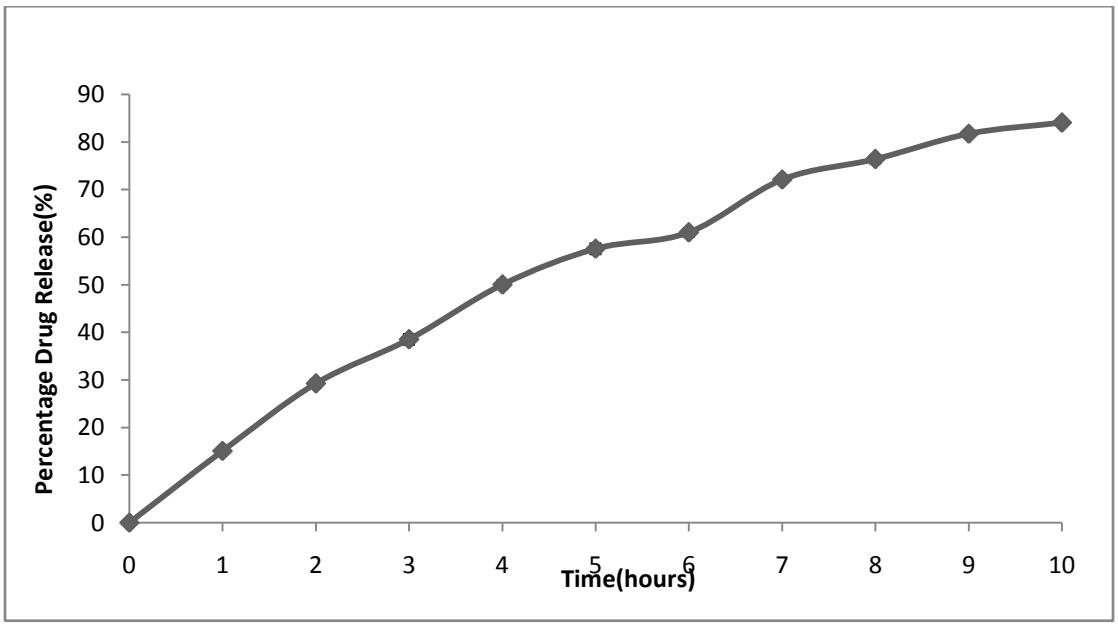


Figure 8.15: *In vitro* drug release profile of formulation VF5

Table 8.18: Dissolution profile of formulation VF6

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	13.39±0.71	12.02	8.01	0.50
2	26.30±0.92	21.48	15.17	0.94
3	35.25±0.46	29.83	21.51	1.38
4	44.73±0.93	37.76	27.40	1.82
5	51.93±0.46	45.16	32.98	2.26
6	59.17±0.93	54.22	38.52	2.80
7	70.16±0.47	60.31	43.93	3.18
8	75.65±0.94	63.31	48.74	3.38
9	82.24±0.69	64.70	52.80	3.49
10	87.33±0.97	66.21	56.25	3.63

*****All values were expressed as mean ±SD, n=3.

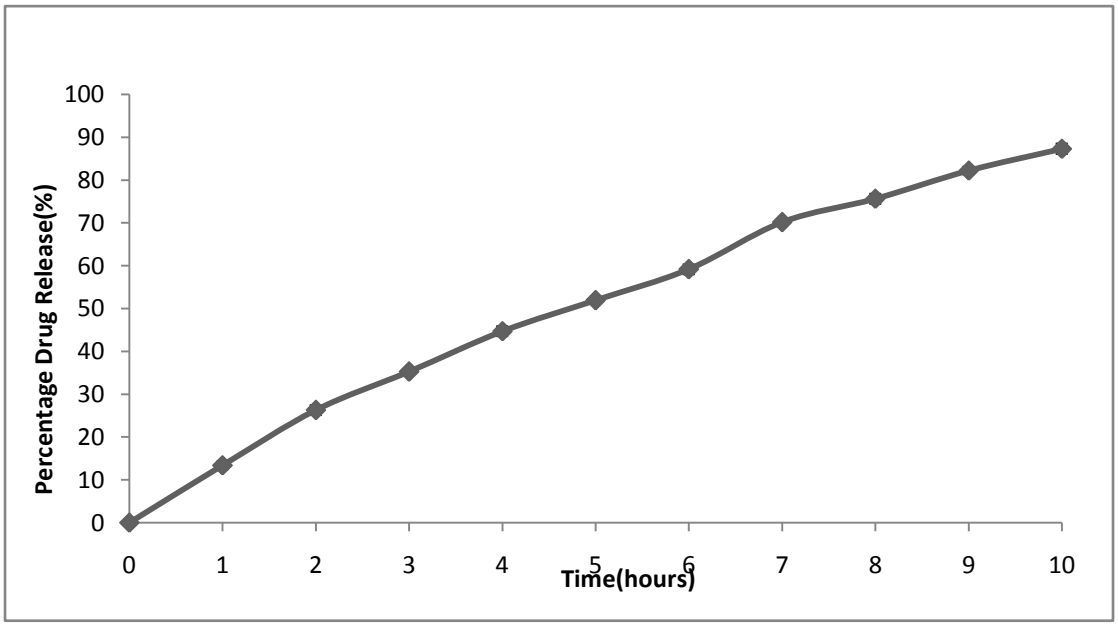


Figure 8.16: *In vitro* drug release profile of formulation VF6

Table 8.19: Dissolution profile of formulation VF7

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	18.95±0.71	10.04	6.70	0.50
2	29.42±0.71	19.72	13.27	0.99
3	37.16±0.94	26.44	19.11	1.37
4	46.18±0.45	33.55	24.33	1.82
5	54.31±0.94	38.95	29.13	2.20
6	63.12±0.69	44.38	33.53	2.60
7	71.81±0.72	52.63	37.98	3.21
8	75.45±0.69	56.74	42.35	3.52
9	80.50±0.70	61.69	46.42	3.92
10	85.88±0.93	65.50	50.25	4.25

*****All values were expressed as mean ±SD, n=3.

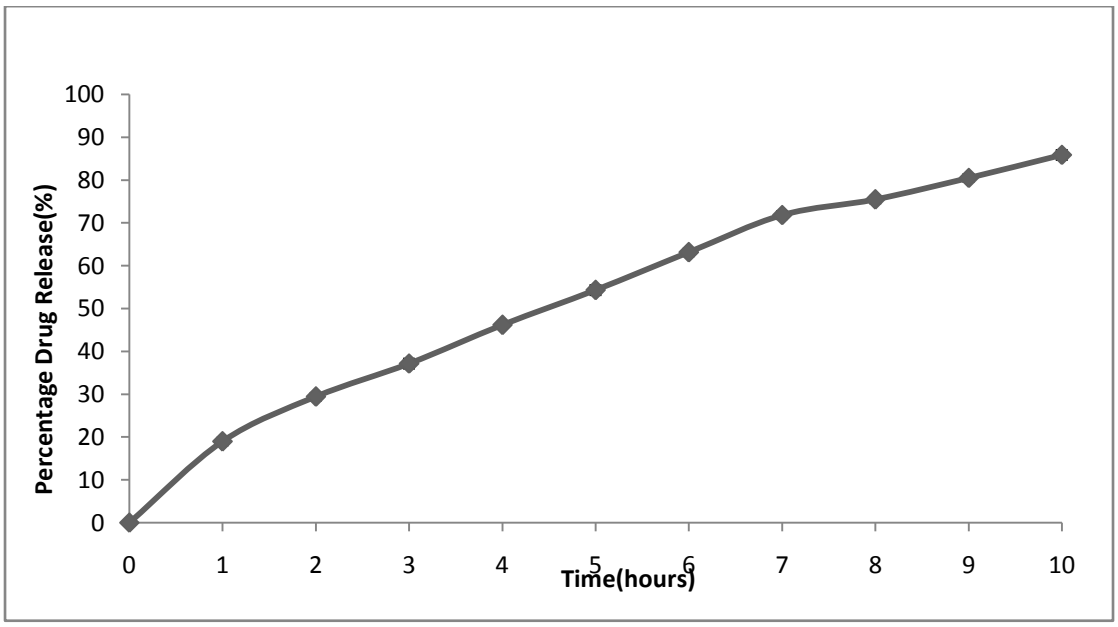


Figure 8.17: *In vitro* drug release profile of formulation VF7

Table 8.20: Dissolution profile of formulation VF8

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	15.71±0.71	14.22	9.48	0.50
2	25.84±0.93	22.07	16.83	0.86
3	33.56±0.72	27.87	22.32	1.20
4	41.32±1.18	34.63	27.16	1.65
5	50.52±0.94	40.74	31.78	2.08
6	62.55±0.73	47.34	36.27	2.55
7	77.58±0.49	53.86	40.72	3.03
8	80.17±0.73	56.59	44.84	3.25
9	84.78±0.74	60.38	48.52	3.58
10	86.47±1.44	64.41	51.99	3.95

*****All values were expressed as mean ±SD, n=3.

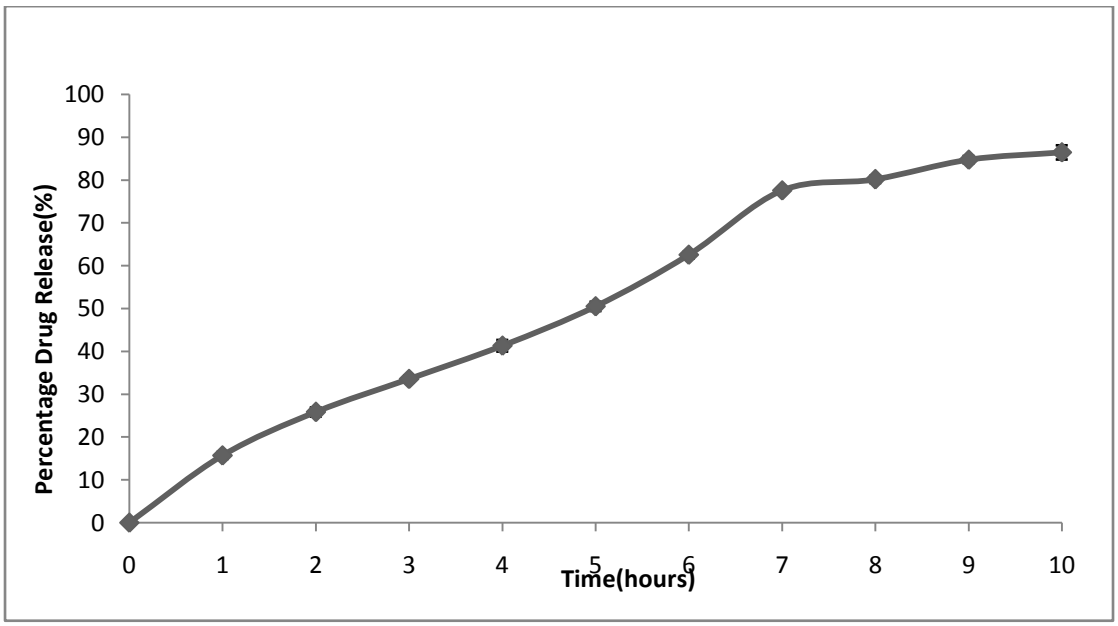


Figure 8.18: *In vitro* drug release profile of formulation VF8

Table 8.21: Dissolution profile of formulation VF9

Time (hours)	Percentage drug released*	Amount (mg)	% DE	MDT
0	0.00±0.00	0.00	0.00	0.00
1	14.93±0.71	11.20	7.47	0.50
2	23.98±0.46	17.99	13.47	0.88
3	30.15±0.93	22.61	18.00	1.21
4	39.75±0.70	29.81	22.24	1.76
5	47.69±0.47	35.77	26.54	2.22
6	59.86±0.96	44.90	31.08	2.89
7	71.17±0.71	53.38	36.00	3.46
8	77.43±0.46	58.08	40.79	3.79
9	82.34±0.71	61.76	45.13	4.07
10	88.50±0.46	66.38	49.16	4.45

*****All values were expressed as mean ±SD, n=3.

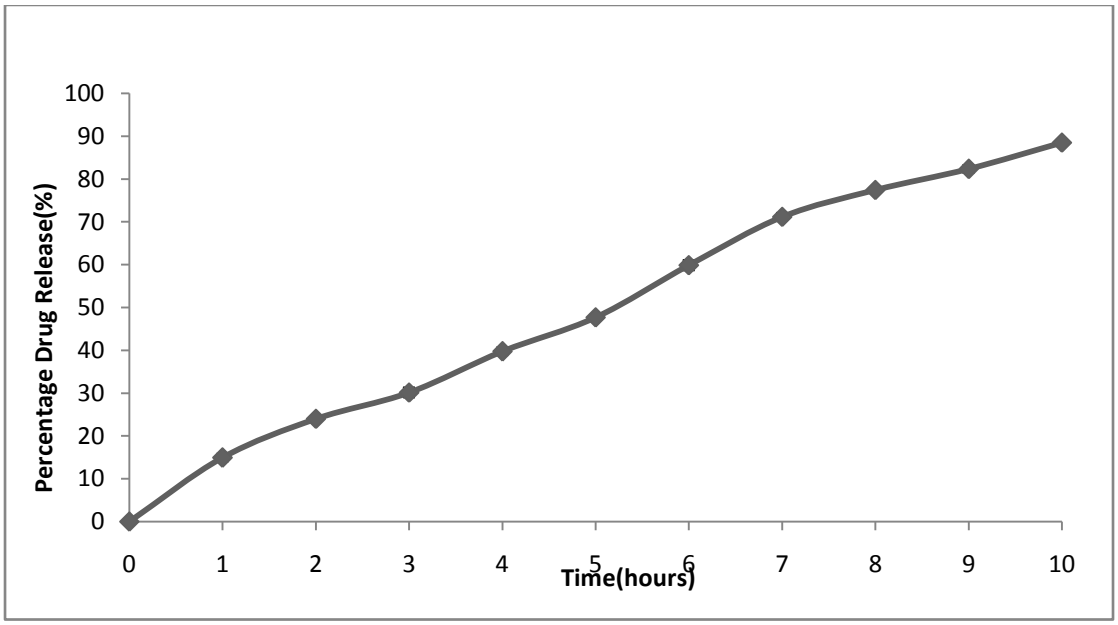


Figure 8.19: *In vitro* drug release profile of formulation VF9

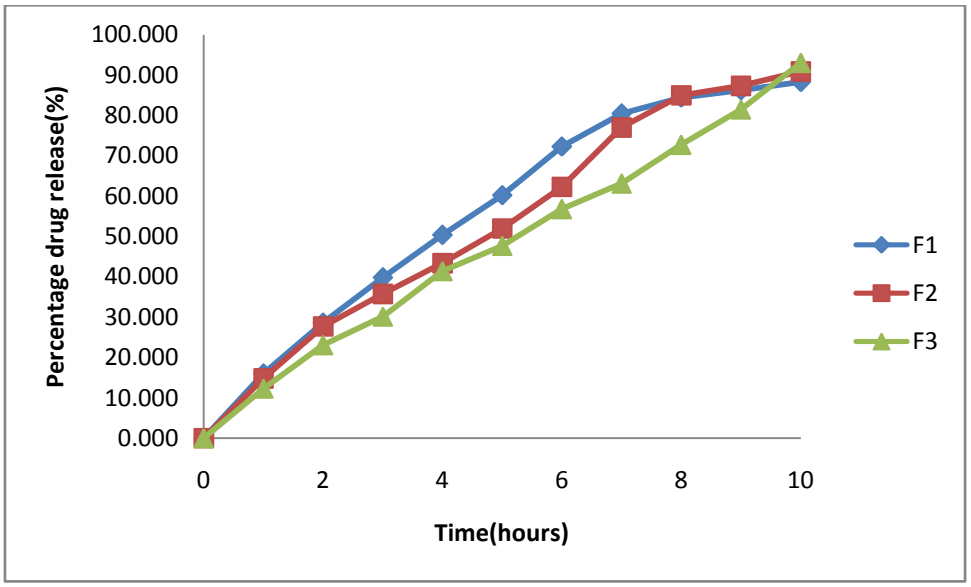


Figure 8.20: *In vitro* drug release profile of formulations containing carnauba wax polymer.

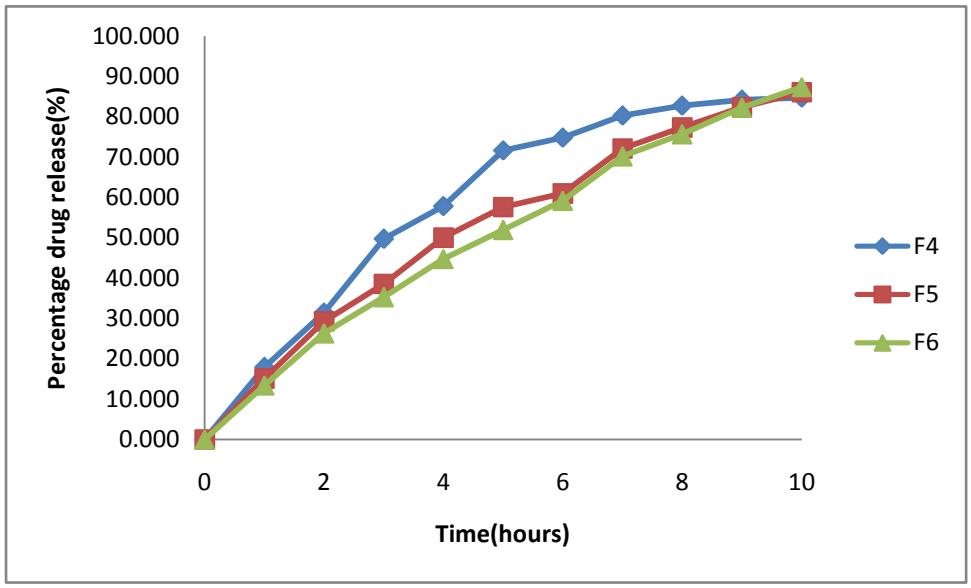


Figure 8.21: *In vitro* drug release profile of formulations containing cetyl alcohol polymer.

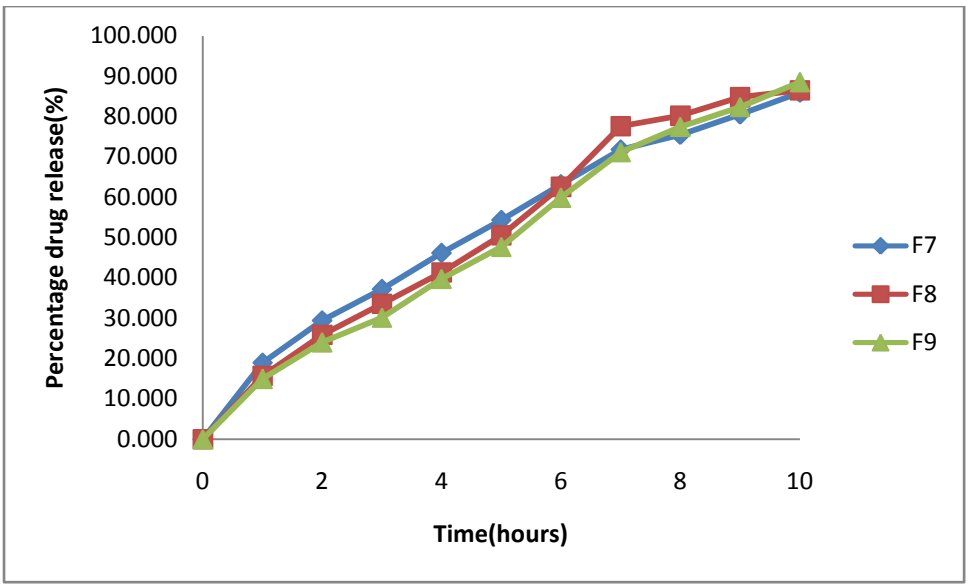


Figure 8.22: *In vitro* Drug Release profile of formulations containing stearic acid polymer.

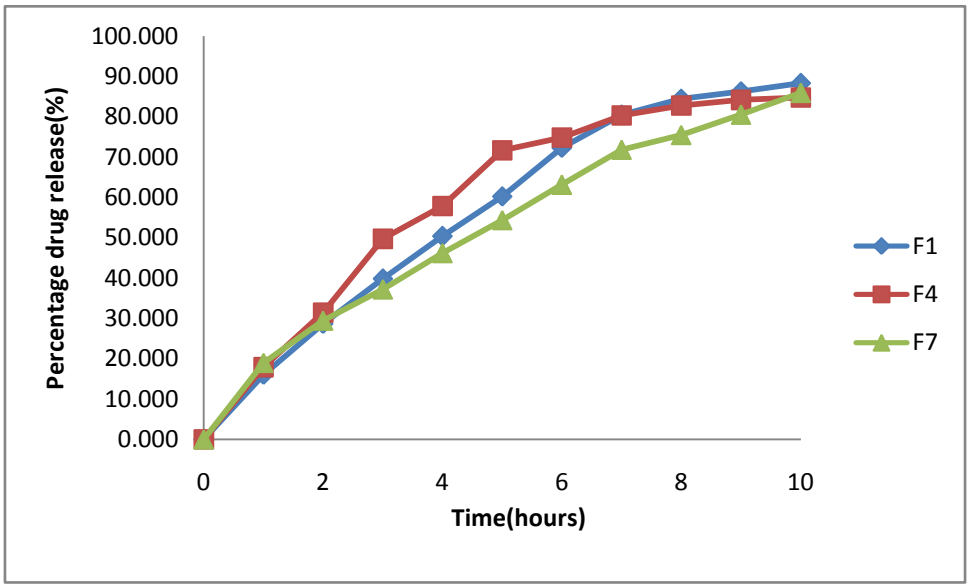


Figure 8.23: *In vitro* drug release profile for different polymers at 15% concentration.

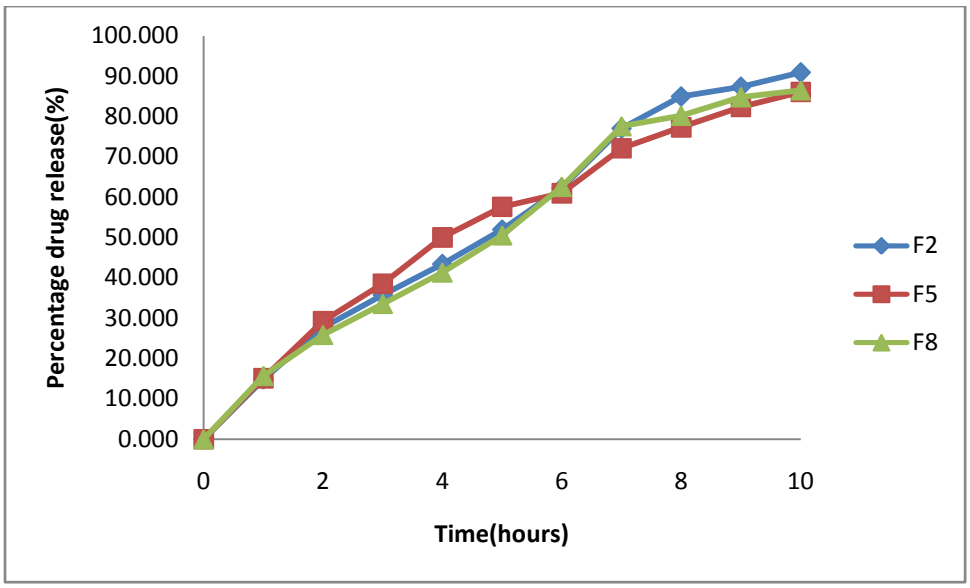


Figure 8.24: *In vitro* drug release profile for different polymers at 30% concentration.

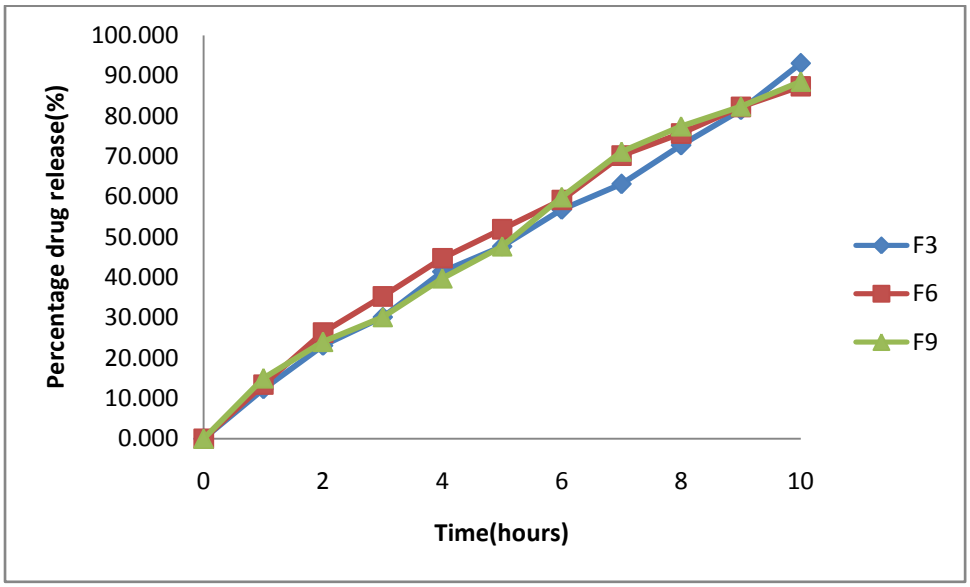


Figure 8.25: *In vitro* drug release profile for different polymers at 45% concentration.

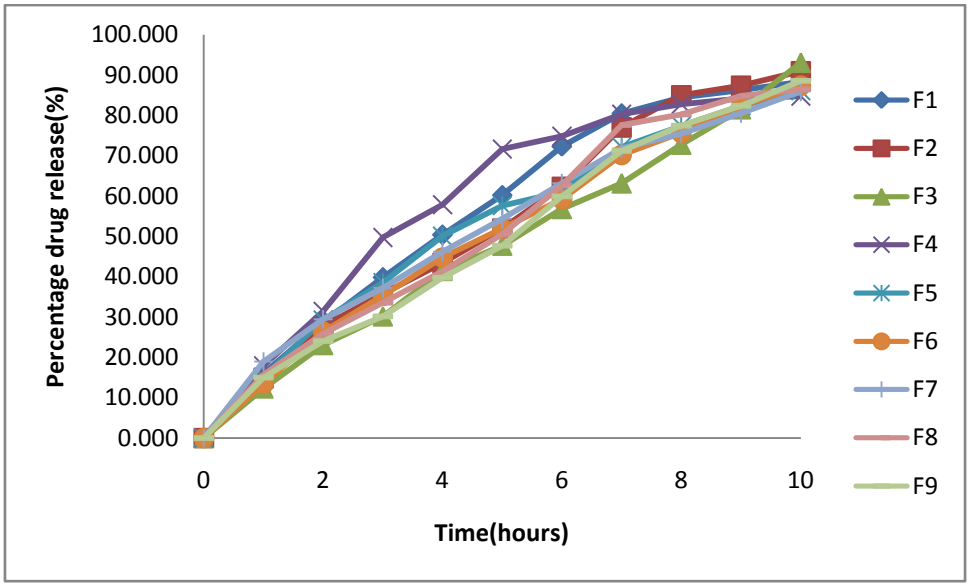


Figure 8.26: *In vitro* drug release profile of VF1 to VF9.

Venlafaxine Hydrochloride drug was soluble in phosphate buffers and its release from the matrix was largely dependent on the polymer swelling, drug diffusion and matrix erosion. The concentration of polymer in the matrix tablet was a key factor in sustaining the drug release.

Various sustained release formulations were formulated with carnauba wax, cetyl alcohol and stearic acid polymer alone and lactose was used as diluents.

The variation in drug release was due to different types of polymers and different concentrations of polymer in all nine formulations. It is expected that the developed formulations should have the following theoretical drug release profile.

The drug released from formulation VF1 to VF3 containing carnauba wax at three concentration levels of 15%, 30%, 45% were found to be 88.27± 1.00, 90.89 ± 0.70, and 93.04 ± 0.45% for Venlafaxine Hydrochloride respectively at the end of 10 hours. It was shown in Tables (8.13, 8.14 and 8.15).

The drug released from formulation VF4 to VF6 containing cetyl alcohol at three concentration levels of 15%, 30%, 45% were found to be 86.07± 1.88, 87.33± 0.97and 85.88± 0.93% for Venlafaxine Hydrochloride respectively at the end of 10 hours . It was shown in Tables (8.16, 8.17 and 8.18).

The drug released from formulation VF7 to VF9 containing stearic acid at three concentration levels of 15%, 30%, 45% were found to be 85.88 ± 0.93, 86.47 ± 1.44 and 88.50± 0.46% for Venlafaxine Hydrochloride respectively at the end of 10 hours. It was shown in Tables (8.19, 8.20 and 8.21).

The drug release rate from carnauba wax matrix was found to be high as compared to cetyl alcohol and stearic acid; it was shown in Figure 8.22. This might be due to slow hydration of matrix and its property to form a thick gel layer, it's due to slow erosion of matrix and its property which retard the drug release from the tablet for long duration.

The overall release rate of Venlafaxine Hydrochloride from cetyl alcohol and stearic acid matrices are significantly lesser than that from carnauba wax matrices were shown in Figure 8.28 and which is confirmed by smaller MDT (2.96, 3.89, 3.63 and 4.25, 3.95, 4.45) respectively for cetyl alcohol and stearic acid and higher MDT for carnauba wax matrices. These results are indicating that carnauba wax has higher drug retarding ability for long duration than cetyl alcohol and stearic acid.

In addition to concentration of polymer, the type and viscosity of polymer also influences drug release. When drug release data obtained from dissolution study of different polymers at 15%, 30% and 45% concentration is plotted against time (Figures 8.23, 8.24 and 8.25) respectively, it was observed that low concentration of polymer induces more drug release. High concentration of polymer should be retarding the drug release for longer period of time.

From the above study, the formulation VF3 was concluded as the best formulation among all the nine formulation of this series. Hence the formulation VF3 was selected for further stability study.

8.3.4. Kinetics of *in vitro* drug release:

In order to investigate the release mechanism, the data were fitted to models representing first order, zero order, higuchi and korsmeyer- Peppas. The linear regression analysis shown as 'r' values in Table 8.22, demonstrated that all the formulated tablets follows korsmeyer- Peppas release kinetics. The result obtained was shown in Figures 8.27 to 8.35.

Table 8.22: Different kinetic models for Venlafaxine Hydrochloride matrix tablets (VF1 to VF9)

F. Code	Zero order	First order	Higuchi	Korsemeyer- Peppas		Best fit model
	R^2	R^2	R^2	R^2	n	
VF1	0.958	0.990	0.975	0.994	0.769	Peppas
VF2	0.984	0.964	0.960	0.996	0.804	Peppas
VF3	0.996	0.912	0.948	0.998	0.859	Peppas
VF4	0.889	0.976	0.980	0.983	0.689	Peppas
VF5	0.962	0.991	0.981	0.994	0.745	Peppas
VF6	0.983	0.979	0.969	0.997	0.804	Peppas
VF7	0.962	0.991	0.983	0.998	0.672	Peppas
VF8	0.980	0.975	0.959	0.994	0.785	Peppas
VF9	0.991	0.966	0.953	0.994	0.807	Peppas

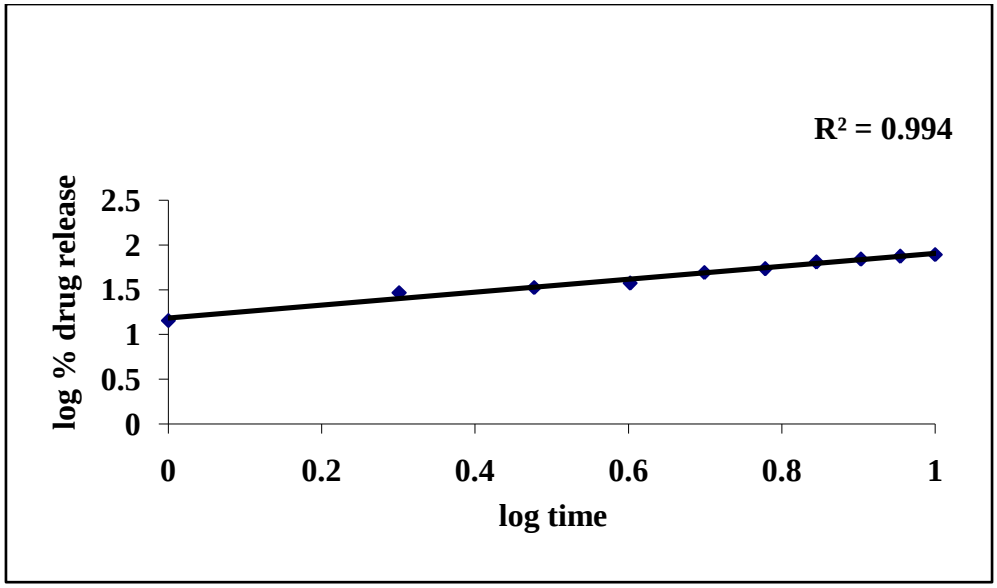


Figure 8.27: Best fit model (Peppas) of formulation VF1

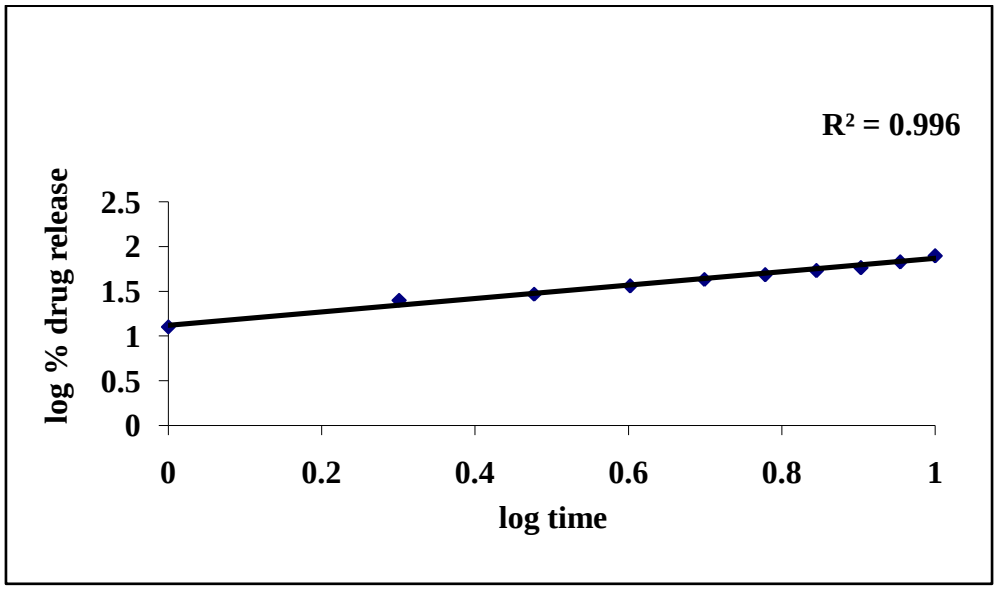


Figure 8.28: Best fit model (Peppas) of formulation VF2

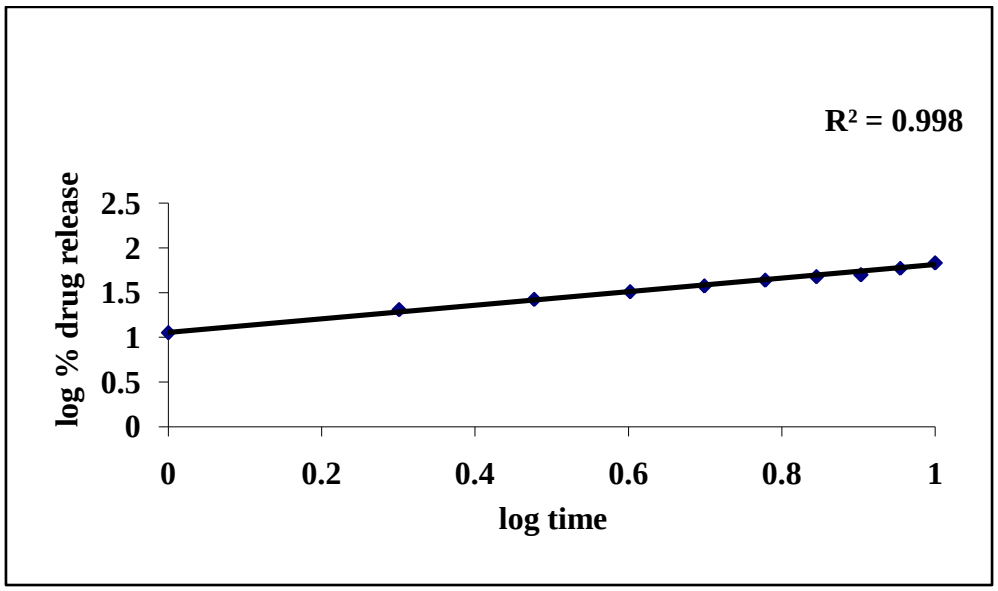


Figure 8.29: Best fit model (Peppas) of formulation VF3

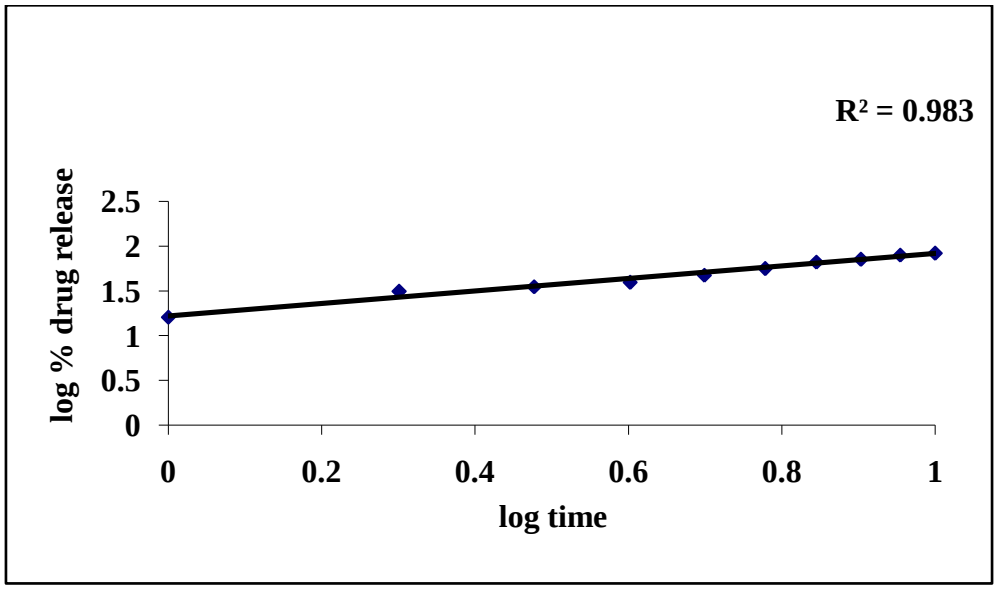


Figure 8.30: Best fit model (Peppas) of formulation VF4

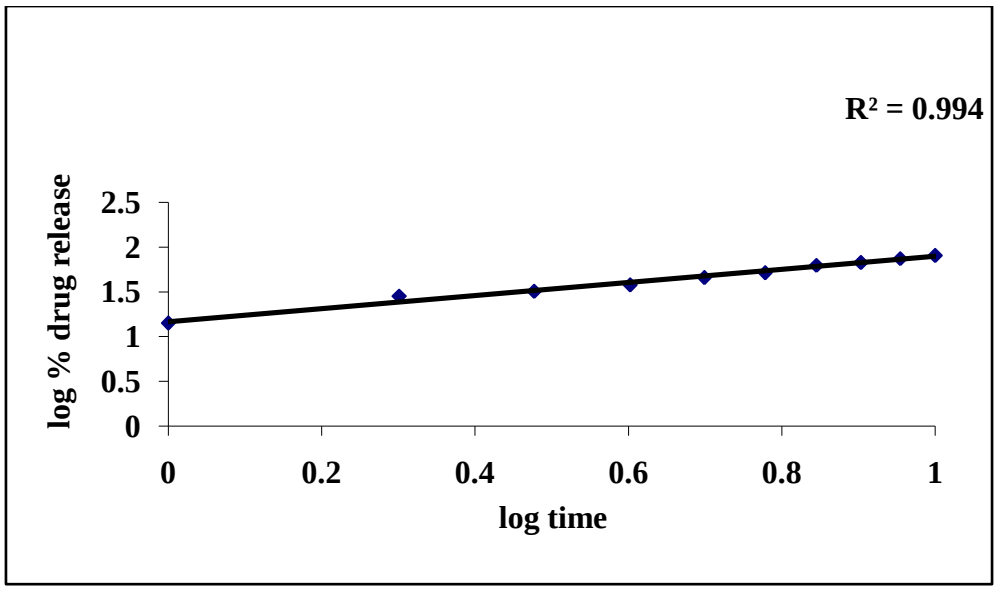


Figure 8.31: Best fit model (Peppas) of formulation VF5

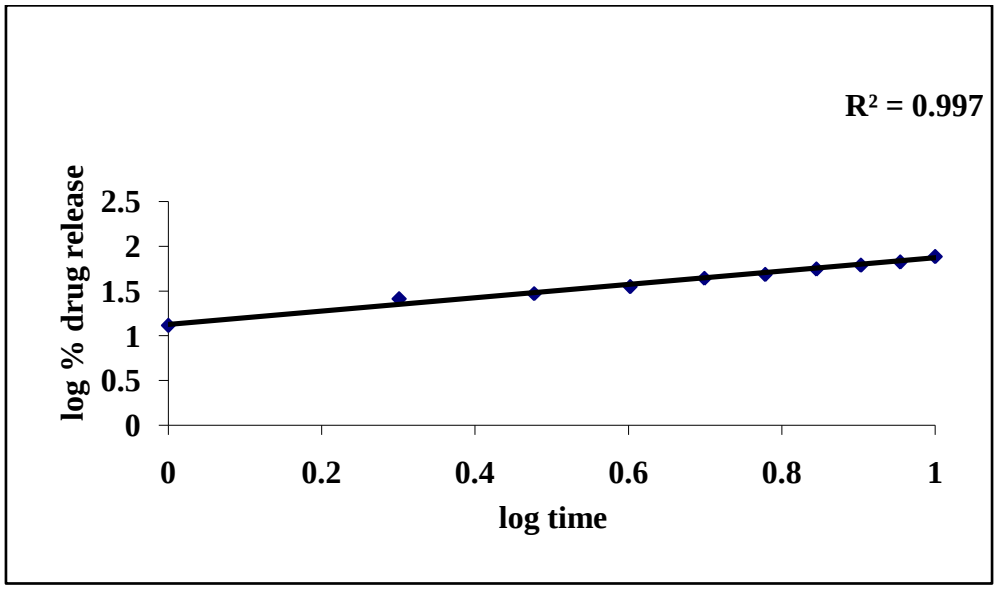


Figure 8.32: Best fit model (Peppas) of formulation VF6

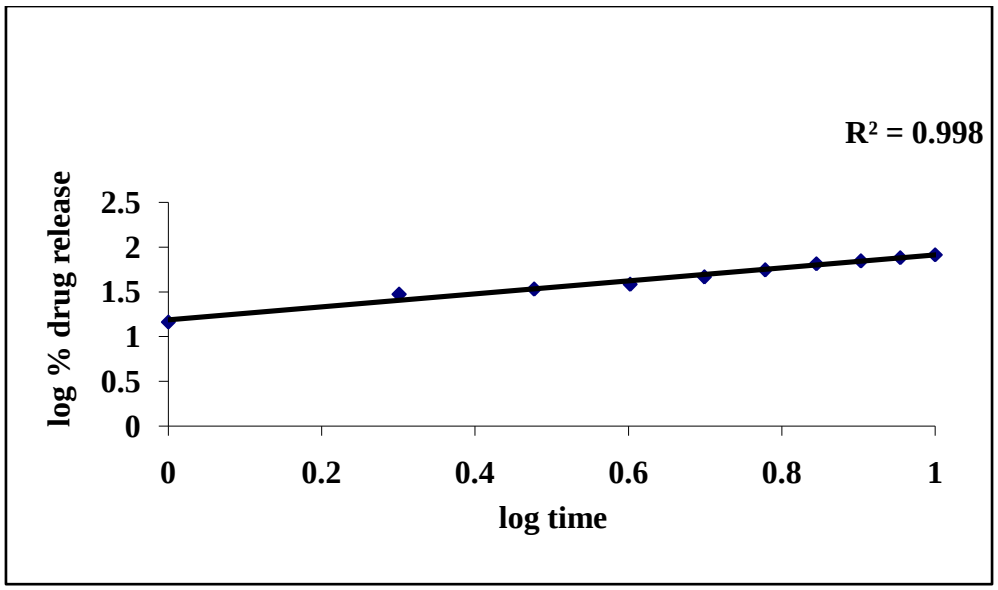


Figure 8.33: Best fit model (Peppas) of formulation VF7

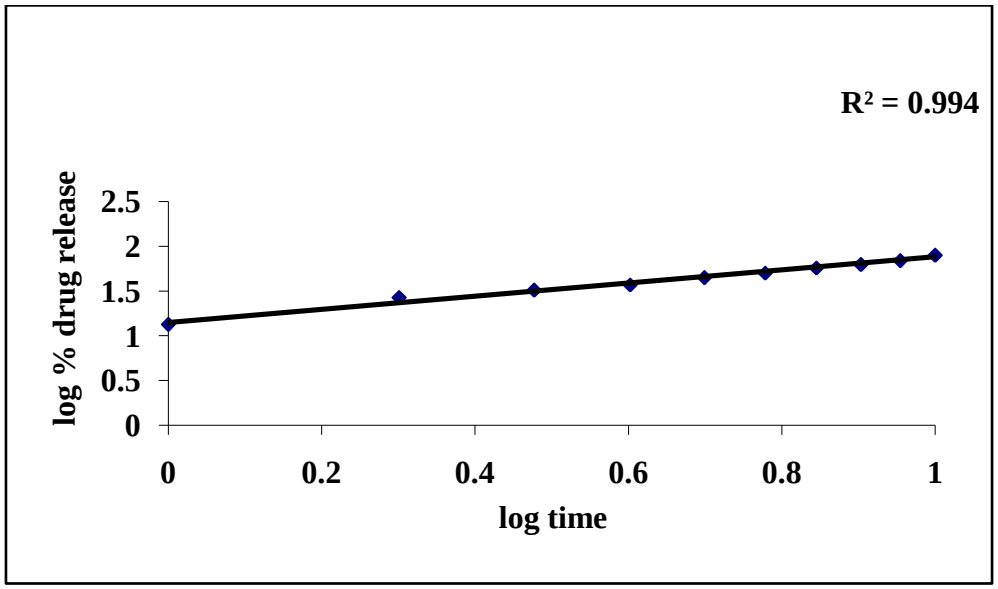


Figure 8.34: Best fit model (Peppas) of formulation VF8

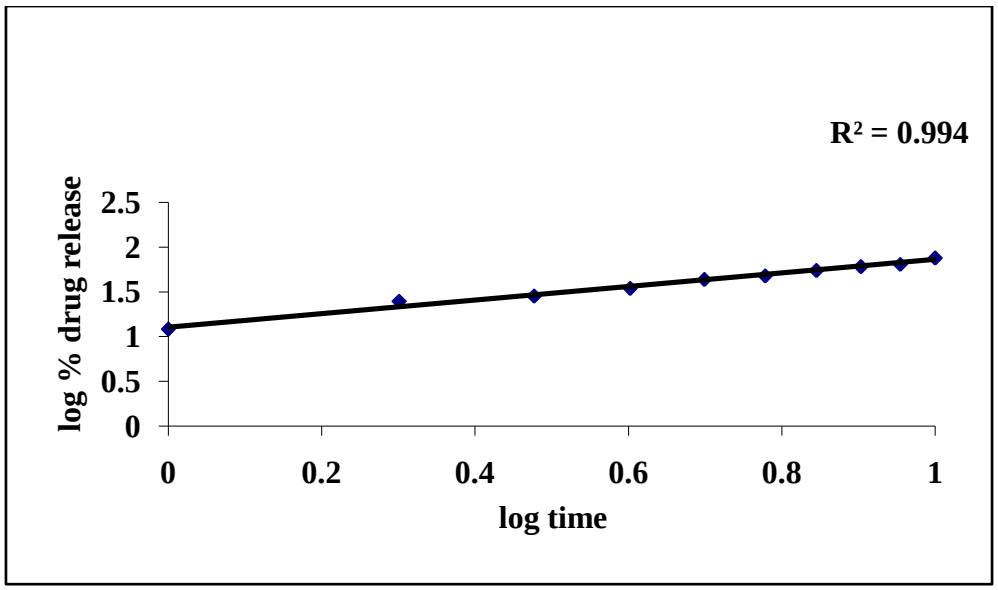


Figure 8.35: Best fit model (Peppas) of formulation VF9

Further, to understand the drug release mechanism, the data were fitted to korsmeyer- Peppas exponent equation, when n < 0.45 indicates fickian drug release. For 0.45 < n < 0.89 as anomalous diffusion (non-fickian). In the present study also it was observed that almost all the formulated tablets followed anomalous diffusion mechanism, which indicates the drug release through diffusion coupled with erosion.

8.4. Stability study:

After exposure to accelerated stability conditions the formulation was analyzed for various evaluation parameters; results were shown in Table 8.23 and Figures 8.36, 8.37, 8.38 and 8.39.

Table 8.23: Stability studies of best formulation VF3 (40°C ± 2°C at 75% ±5%)

Characteristic	Initial	1st Month	2nd Month	3rd Month
Appearance*	Pale yellow	No change	No change	No change
Hardness (kg/cm^2)*	7.10±0.02	7.05±0.01	7.00±0.03	6.95±0.01
Friability (%)*	0.085±0.05	0.083±0.03	0.081±0.01	0.080±0.02
Drug content (%)*	99.75±0.11	99.61±0.23	99.43±0.10	99.12±0.14
In vitro* drug release at the end of 12 hours	93.04±0.45	92.86±0.31	92.60±0.27	92.37±0.16

*All the values were expressed as mean ± SD; n=3

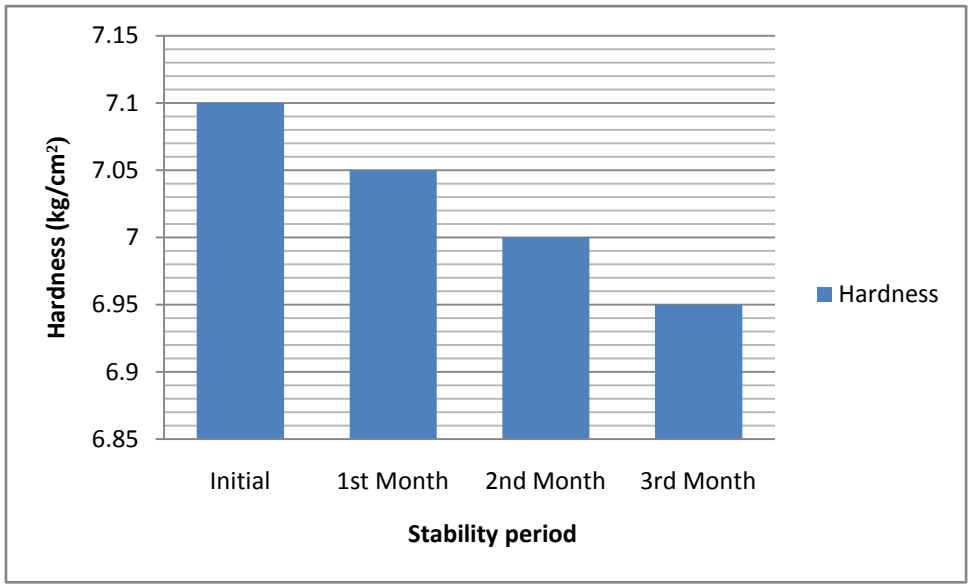


Figure 8.36 : Comparison for hardness of before and after stability studies of best formulation VF3.

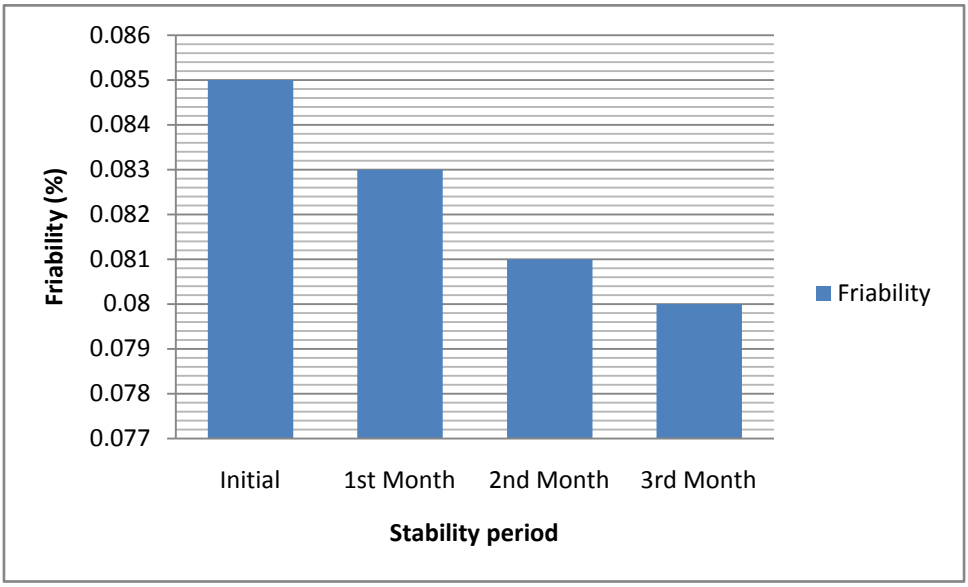


Figure 8.37 : Comparison for friability of before and after stability studies of best formulation VF3.

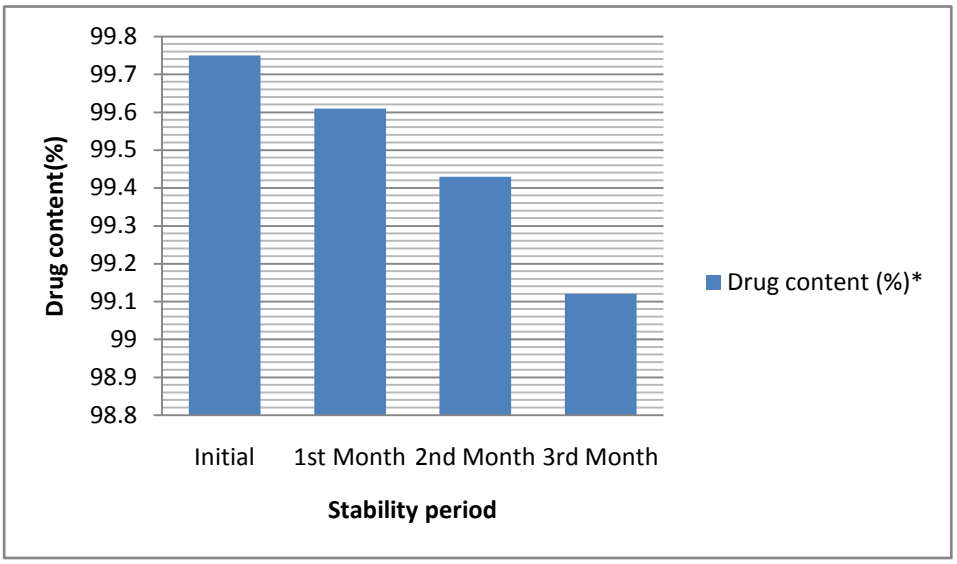


Figure 8.38: Comparisons for drug content of before and after stability studies of best formulation VF3.

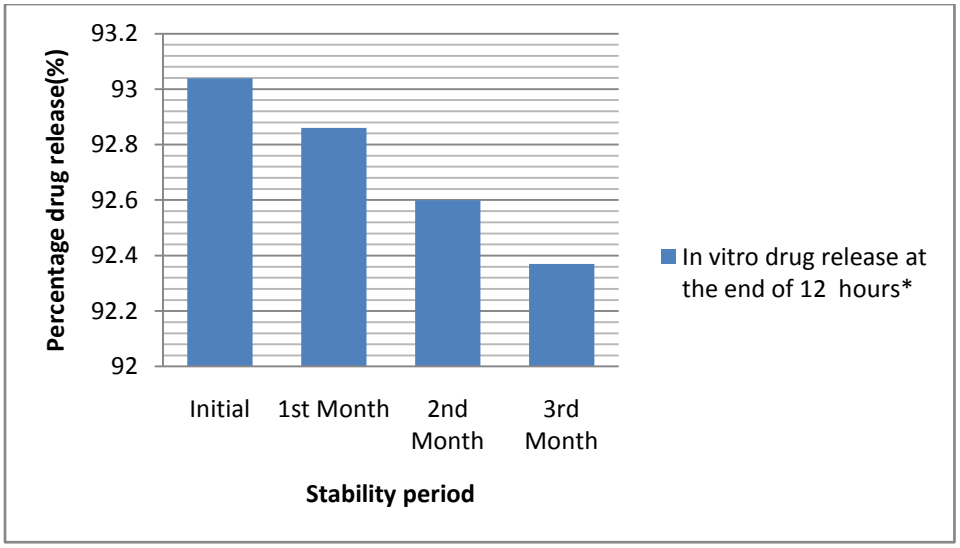


Figure 8.39: Comparisons for *in vitro* drug release profile of before and after stability studies of best formulation VF3.

From the above studies there was no significance differences was initiate between the evaluated data from initial and after stability studies and all the values were found in worth accepting limits. The best formulation was showed adequate physical stability at 40^{o}C ± 2^{o}C at 75% ± 5% relative humidity.

SUMMARY AND CONCLUSION

9. SUMMARY AND CONCLUSION

Oral route has been the commonly adopted and most convenient route for the drug delivery. Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes. The oral route of delivery is perhaps the least invasive method of delivering drugs, it's a route that the patient understand and accepts, patient are able to administer the medicine to themselves. For the manufacturer, solid oral dosage form offer many advantages; are generally the most stable forms of drugs, are compact and their appearance can be modified to create brand identification.

Venlafaxine Hydrochloride was chosen as a drug having soluble in intestinal pH. Venlafaxine Hydrochloride plays a major role in treatment of depression. It acts as a serotonin-norepinephrine-dopamine reuptake inhibitor. The drug half-life in plasma is 5 hours. It is bound to plasma protein about 27%. Venlafaxine Hydrochloride is well absorbed with a bioavailability of 45% following oral ingestion, hence it was considered as an good candidate for the design of oral sustained release dosage form.

In the present study, an attempt was made to formulate the oral sustained release matrix tablets of Venlafaxine Hydrochloride to provide a dosage form for prolonged period of time, in order to improve efficacy, reduce the frequency of total

dose and better patient compliance. Infrared spectroscopy and differential scanning calorimetric analysis confirmed the absence of any drug polymer interaction.

The sustained release matrix tablets were prepared by Hot melt granulation method using different polymers like carnauba wax, cetyl alcohol and stearic acid as release retardant polymers. The granules were evaluated for angle of repose, bulk density, compressibility index and hausner's ratio. All the tests revealed that granules showed excellent flow properties.

The resulting monolithic tablets were evaluated for thickness, diameter, weight variation test, hardness, friability and drug content. All the tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopoeial standards. The *in vitro* release profiles from tablets of drug and different polymer ratio were applied on various kinetic models. *In vitro* release studies revealed that the release rate was decreased with increase in polymer proportion.

In the present studies, matrix formulation VF3 containing Carnauba wax were probably showing maximum retardation of drug release and it shows anomalous diffusion mechanism, for these reasons, it was considered that the formulation VF3 as best formulation among all the nine formulations. Based on release exponent (n) values, it was concluded that mechanism of drug release was found to be diffusion coupled with erosion (anomalous transport mechanism).

From the stability studies, there was no significance difference in hardness, friability, drug content and *in vitro* release profile for the best formulation.

FUTURE PROSPECTS

10. FUTURE PROSPECTS

In the present work, the sustained release matrix tablets of Venlafaxine Hydrochloride were prepared by Hot melt granulation technique using carnauba wax, cetyl alcohol and stearic acid as release retardant polymers.

In this work, only physiochemical characterization such as angle of repose, Carr's index, hausner ratio, weight variation, hardness, thickness, friability, drug content and *in vitro* evaluation of matrix tablet of Venlafaxine Hydrochloride was performed. Along with *in vitro* studies, *in vivo* studies of drug is most important.

In future *in vivo* studies are required to set the *in vitro* - *in vivo* correlation (IVIVC) which is necessary for development of successful formulation and also long term stability studies are necessary.

BIBLIOGRAPHY

11. BIBLIOGRAPHY

1) Amelia Avachat and Vikram Kotwal. Design and Evaluation of Matrix-Based Controlled Release Tablets of Diclofenac Sodium and Chondroitin Sulphate, *AAPS Pharm. Sci. Tech*., **2007**, 8(4), 1-6.
2) Anonymous, http://en.wikipedia.org/wiki/Venlafaxine.
3) Anonymous, http://www.about cnsforum.com/Venlafaxine
4) Anonymous, http://www.about.Com
5) Anonymous, http://www.chemicalbook.com/Venlafaxine
6) Anonymous, http://www.drugbank.Ca/Drugs/DB00285.
7) Anonymous, http://www.drugs.com/Venlafaxine.html.
8) Anonymous, http://www.pharmainfo.net.
9) Anonymous, Indian Pharmacopoeia. Government of India Ministry of Health and Family Welfare, The Indian Pharmacopoeia Commission, Ghaziabad, India, **2007**, 1, 142-143.
10) Anonymous, The Merck Index. An Encyclopedia of Chemicals, Drugs & Biologicals. 14th edn, Merck & Co. Inc, New Jersy, USA. **2006,** 9946.
11) Ansel H.C., Allen L.V. and Popovich N.G. Pharmaceutical Dosage Forms and Drug Delivery System, 4th edn., Lippincott Williams and Wilkins, New Delhi, **2009**, 227-274.

12) Atul A. Bodkhe., Prashant Zurao., A.V. Chandewar and S.B.Jaiswal. Designing and Evaluation of Extended Release Tablet of Venlafaxine Hydrochloride using Hydrophobic matrix, *Scholars Research Library.*, **2010**, 2(1), 329-335.

13) Aulton M.E. Pharmaceutics: The Design and Manufacture of Medicine, 3rd edn., Churchill Livingstone, New York, **2007**, 355-359,483-498.

14) Bagdiya S Om Prakash., Sar Ajay., Gejoge Santosh and Purnima Amract. Formulation and Development of Venlafaxine Hydrochloride Extended Release Tablet and *In vitro* Characterizations, *International Journal of Pharm Tech Research.,* **2012**, 4(4), 1777-1784.

15) Banker G.S. and Rhodes C.T. Modern Pharmaceutics, 4th edn., Informa Health Care USA, Marcel Dekker, Inc, New York, **2009**, 501-514.

16) Bhalekar.R., A.R.madgulkar.,D.D.Sheladiya and S.S.Desale.Althaf A.S. Stastical optimization of Sustained Release Venlafaxine Hydrochloride wax matrix Tablets, *Indian Journal of Pharmaceutical Sciences.*, **2008**, 70(4), 472-476.

17) Brahmankar D.M. and Jaiswal S.B. Biopharmaceutics and Pharmacokinetics A Treatise, 2nd edn., Vallabh Prakashan, New Delhi, **2009**, 397-452.

18) Carstensen J.T. and Rhodes C.T. Drug Stability Principles and Practices, 3rd edn., Marcel Dekker, Inc, New York, **2008**, 415-481.

19) Chein Y.W. Novel Drug Delivery System, 2nd edn., Revised and Expanded. Marcel Dekker, Inc, New York, **2009**, 139-196.

20) Deepak S. and Rana A.C. Formulation Development of Quetiapine Fumarate SR Matrix Tablets, *Pelagia Research Library.*, **2010**, 1(1), 48-57.

21) Gohel M.C., Parikh R.K. and Padshala M.N. Formulation and Optimization of Directly Compressible Isoniazid Modified Release Matrix Tablet, *Indian Journal of Pharmaceutical Sciences.*, **2007**, 69(5), 640-645.

22) Goodman and Gilman's. The Pharmacological Basis of Therapeutics, 10th edn., Harman J.G. and Limbird L.E, New York, **2001**, 1349-1359.

23) Harris Shoaib M., Tazeen J., Merchant H.A. and Yosuf R.I. Evaluation of Drug Release Kinetics from Ibuprofen Matrix Tablets Using HPMC, *Pak. J. Pharm. Sci.*, **2006**, 19(2), 119-124.

24) Indranil Kumar Yadav and Singh H.P. Formulation, Evaluation and Optimization of Aceclofenac Sustained Release Matrix Tablets, *International Journal of Pharm Tech Research.*, **2010**, 2(1), 592-598.

25) Kalyani C., and Prabhakar R.V. Formulation and Evaluation of Zidovudine Sustained Release Matrix Tablets, *J. Pharm. Res.*, **2009**, 2(6), 1031-1034.

26) Lachman L., Lieberman H.A. and Kanig J.L. The Theory and Practice of Industrial Pharmacy, 4th edn., Varghese Publishing House, Mumbai, **1991**, 88,293-345.

27) Madhusmruti K., Santanu C., Anuradha S., Debashisha P., Nazia K. and Santosh K.P. Development of Propranolol Hcl Matrix Tablets: An Investigation on Effects of Combination of Hydrophilic and Hydrophobic Matrix Former Using Multiple Compression Analysis, *Int. J. Pharm. Sci. Rev And Res.*, **2010**, 1(2), 1-7.

28) Manavalan R. and Ramasamy S. Physical Pharmaceutics, 2nd edn., Vignesh Publisher, Chennai, **2001**, 288-299.

29) Mukesh C. Gohel and Shital H.Bariya. Fabrication of Triple- Layer Matrix Tablets of Venlafaxine Hydrochloride, *AAPS Pharmaceutical Sciences Technology.*, **2009**, 10(2), 624-630.

30) Nikil A Karani and Prashant pingale. Analytical Method Development and Validation of Venlafaxine Hydrochloride in Solid Dosage Form using UV Spectrophotometer, *Journal of Pharmacy Research.*, **2009**, 2, 1246-1249.

31) Patil U.K., Sourabh Jain and Yadav S.K. Preparation and Evaluation of Sustained Release Matrix Tablet of Furosemide Using Natural Polymers, *Research J. Pharm. And Tech.*, **2008**, 374-376.

32) Potu Apparao, Jyothi and Veerareddy Prabhakar Reddy. Formulation and Evaluation of Gum Based Matrix Tablets of Lamivudine, *Pelagia Research Library.*, **2011**, 2 (3), 176-192.

33) Prabu Moses, Subramanian L. and Palanichamy S. Formulation and Evaluation of Ciprofloxacin Controlled Release Matrix Tablets, *Scholars Research Library.*, **2010**, 2(2), 237-243.

34) Radhika P R., Dedeepya Karanam and Sivakumar T. Fabrication of Sustained Release Matrix Tablets of Venlafaxine Hydrochloride Using Eudragits, *International Journal of Research in Ayurveda and Pharmacy.*, **2011**, 2(4), 1386-1389.

35) Raghuram Reddy K., Srinivas M. and Srinivas R. Once Daily Sustained Release Matrix Tablets of Nicorandil: Formulation and *In Vitro* Evaluation, *AAPS Pharm. Sci. Tech.*, **2003**, 4(4), 1-9.

36) Raju M., Sundaramoorthy K. and Vetrichelvan T. Formulation and In-Vitro Evaluation of Sustained Release Matrix Tablets of Aceclofenac by Using

Different Natural Polymers, *Research Journal of Pharmaceutical, Biological and Chemical Sciences.*, **2010**, 1(4), 279-291.

37) Raymond C Rowe, Paul J Sheskey and Marian E Quinn. Handbook of Pharmaceutical Excipients, 6th edn., Pharmaceutical Press, London, **2009**, 155, 697,772.

38) Saleh M. Al-Saidan, Yellela S. R. Krishnaiah and Srinivas S. Patro. In-Vitro and In-Vivo Evaluation of Guar Gum Matrix Tablets for Oral Controlled Release of Water-Soluble Diltiazem Hydrochloride, *AAPS Pharm. Sci. Tech*., **2005**, 6 (1), 1-8.

39) Sandip B.T., Krishna Murthy T., Raveendra Pai M., Pavak R.M. and Pasula B.C. Controlled Release Formulation of Tramadol Hydrochloride Using Hydrophilic and Hydrophobic Matrix System, *AAPS Pharm. Sci. Tech*., **2003**, 4(3), 1-7.

40) Saravanabhavan Shanmugam, Rajappan Manavalan and Devashya Venkappayya. Release Kinetics Studies of Aceclofenac from Sustained Release Matrix Tablets, *Journal of Pharmacy Research.*, **2010**, 3(11), 2725-2727.

41) Seema Pushkar and Nikhil K. Sachan. Pharmaceutical Characterization and Assessment of Drug Release Behaviour of Diclofenac Sodium Extended Release Matrix Devices, *Int. J. Pharm. Sci. Tech*., **2009**, 2(1), 14-21.

42) Silverstein R.M. and Webster F.S. Spectrometric Identification of Organic Compounds, VI edn., John Wiley and Sons, Inc. USA, **2003**, 71-144.

43) Skoog D.A., Holler F.J. and Crouch S.R. Fundamental of Analytical Chemistry, 8th edn., Thomson Asia Pvt. Ltd., Singapore, **2004**, 775-781, 811-819.

44) Sreenivasa rao K., Jadhav Sunita and Patil Prakash. Development and evaluation of Sustained Release Formulations of Venlafaxine Hydrochloride, *International Research Journal of Pharmacy.,* **2011,** 2(5), 261-270.

45) Sundaramoorthy K., Kavimani S. and Swaminathan S. Development and Evaluation of Extended Release Metformin Hydrochloride Matrix Tablets: Rate of *In-Vitro* and *In-Vivo* Release Studies, *Journal of Pharmacy Research.,* **2011**, 4(3), 884-885.

46) Vimal Dshirvi., Vijayakumar G. and channabasavaraj K.P. Third Order Derivative Spectrophotometric Estimation of Venlafaxine Hydrochloride in Bulk and Pharmaceutical Formulations, *International Journal of Pharma Technology and Research.,* **2010**, 2, 700-703.

47) Vyas S.P. and Khar R.K. Controlled Drug Delivery, 1st edn., Vallabh Prakashan, New Delhi, **2002**, 1-36, 97-151, 164-170.

48) Willard H.H., Merritt L.L. and Settle F. A. Instrumental Methods of Analysis, 12th edn., CBS Publishers and Distributors, New Delhi, **2008**, 762-766.